Multiple-Component Reactions in Optical Biosensors

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Overview

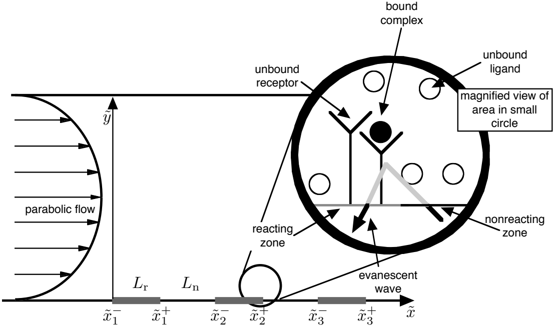
- What are optical biosensors and surface-volume reactions?
- Can we develop an accurate mathematical model for multiple-component reactions in optical biosensors?
- Given a set of data, can we determine the associated reaction rates?
- How does the reacting species behave in the single ligand case, when there exists a *strong nonlinearity* in the governing equation.

Introduction

- Many chemical reactions in biology involve a stream of chemical reactants (*ligand*) flowing through a fluid-filled volume, over a surface to which other reactants (*receptors*) are confined.
- These surface-volume reactions occur in a number of biological processes such as blood clotting, drug absorption, DNA-damage repair.

Optical Biosensor

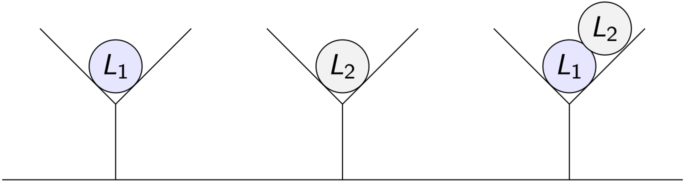
- Optical biosensors are a popular way to measure such reactions without disturbing the underlying system.



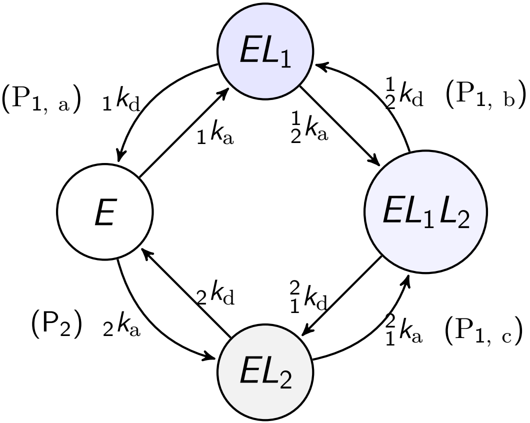
Multiple-Component Reactions

- This process has been well studied in the reaction limited, transport dominant (*weakly nonlinear*) parameter regime, when there is only a single ligand.
- What happens when there are multiple reactions on the suface?

Multiple-Component Reactions



Multiple-Component Reactions



Multiple-Component Reactions in Optical Biosensors

- Having an accurate mathematical model of this process helps interpret biosensor data.
- Biosensor only measure on a weighted average of reacting species concentrations.

Multiple-Component Reactions in Optical Biosensors

- Biosensor only measures on a weighted average of reacting species concentrations

$$S(t) := \frac{1}{x_{\max} - x_{\min}} \int_{x_{\min}}^{x_{\max}} B_1(x,t) + \left(1 + \frac{\rho_2}{\rho_1}\right) B_{12}(x,t) + \frac{\rho_2}{\rho_1} B_2(x,t)\, \mathrm{d}x$$

Here B_i are reacting species concentrations

$$\begin{aligned} B_1(x,t) &= [EL_1](x,t), \\ B_2(x,t) &= [EL_2](x,t), \\ B_{12}(x,t) &= [EL_1 L_2](x,t) \end{aligned}$$

ρ_i are molecular weights of B_i.

Multiple-Component Reactions in Optical Biosensors

- Can rewrite

$$S(t) = \frac{1}{x_{\max} - x_{\min}} \int_{x_{\min}}^{x_{\max}} B_1(x,t) + \left(1 + \frac{\rho_2}{\rho_1}\right) B_{12}(x,t) + \frac{\rho_2}{\rho_1} B_2(x,t)\,\mathrm{d}x$$

more compactly as:

$$S(t) = \overline{B}_1(t) + \left(1 + \frac{\rho_2}{\rho_1}\right) \overline{B}_{12}(t) + \frac{\rho_2}{\rho_2} \overline{B}_2(t),$$

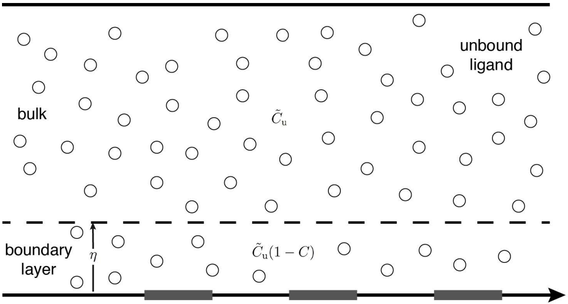
$$\overline{B}_i = \frac{1}{x_{\max} - x_{\min}} \int_{x_{\min}}^{x_{\max}} B_i(x,t)\,\mathrm{d}x.$$

Mathematical Model

- Convection-diffusion equations for each of the unbound ligands $C_1(x, y, t) = [L_1](x, y, t)$, $C_2(x, y, t) = [L_2](x, y, t)$.
- Coupled to a system of PDE's describing the evolution of the reacting species concentration B_i at the boundary.

Two Compartment

- High flow rate and slow diffusion results means that diffusion is only important in a layer near the boundary, *e.g.* several time scales and boundary layers.



Mathematical Model

$$\frac{\partial C_1}{\partial t_c} = (\mathrm{D}_r \mathrm{Pe}^{-1}) \left(\epsilon^2 \frac{\partial^2 C_1}{\partial x^2} + \frac{\partial^2 C_1}{\partial y^2} \right) - y(1-y) \frac{\partial C_1}{\partial x}, \quad (1)$$

$$\frac{\partial C_2}{\partial t_c} = \mathrm{Pe}^{-1} \left(\epsilon^2 \frac{\partial^2 C_2}{\partial x^2} + \frac{\partial C_2}{\partial y^2} \right) - y(1-y) \frac{\partial C_2}{\partial x}. \quad (2)$$

- t_c is the convective time scale.
- $\mathrm{Pe} \gg 1$, $\epsilon \ll 1$[1].
- D_r is the ratio of the diffusivity of the two ligands, order one.
- Parabolic velocity profile.

[1] $\mathrm{Pe} = 3.71 \times 10^2, \ \epsilon = 2.08^{-2}$

Initial and Boundary Data

- Initial conditions: $C_j(x, y, 0) = 0$.
- Inflow condition: $C_j(0, y, t) = 1$.
- No change in the concentration as it exits the channel $\frac{\partial C_j}{\partial x}(1, y, t) = 0$.
- No flux through the ceiling $\frac{\partial C_j}{\partial y}(x, 1, t) = 0$.

Bottom Boundary Condition

- Diffusive flux conditions:

$$D_r D \frac{\partial C_1}{\partial y}(x,0,t_c) = \frac{\partial B_1(x,t_c)}{\partial t_c} + \frac{\partial B_{12}(x,t_c)}{\partial t_c}$$
$$D \frac{\partial C_2}{\partial y}(x,0,t_c) = \frac{\partial B_{12}(x,t_c)}{\partial t_c} + \frac{\partial B_2(x,t_c)}{\partial t_c}$$

- $D = \frac{\text{Diffusion rate from channel to reacting surface}}{\text{Convective Transport in Channel}}$.
- $D \ll 1 \Rightarrow$ bound state governed by slower diffusive processes.
- Need another set of equations for B_i.

Reaction Kinetics

$$
\begin{aligned}
\frac{\partial B_1}{\partial t_c} &= {}_1k_\mathrm{a}(1 - B_\Sigma)C_1 + {}^1_2k_\mathrm{d}B_{12} - {}_1k_\mathrm{d}B_1 - {}^1_2k_\mathrm{a}B_1C_2, \\
\frac{\partial B_{12}}{\partial t_c} &= {}^1_2k_\mathrm{a}B_1C_2 + {}^2_1k_\mathrm{a}B_2C_1 - {}^1_2k_\mathrm{d}B_{12} - {}^2_1k_\mathrm{d}B_{12}, \\
\frac{\partial B_2}{\partial t_c} &= {}^2_1k_\mathrm{d}B_{12} + {}_2k_\mathrm{a}(1 - B_\Sigma)C_2 - {}^2_1k_\mathrm{a}B_2C_1 - {}_2k_\mathrm{d}B_2, \\
B_\Sigma &= B_1 + B_{12} + B_2
\end{aligned}
$$

- $1 - B_\Sigma$ empty receptor concentration
- Initially no bound ligand $B_1(x,0) = B_{12}(x,0) = B_2(x,0) = 0$,

Reaction Kinetics

$$\frac{\partial B_1}{\partial t_c} = {}_1k_\mathrm{a}(1 - B_\Sigma)C_1 + {}^1_2k_\mathrm{d}B_{12} - {}_1k_\mathrm{d}B_1 - {}^1_2k_\mathrm{a}B_1C_2, \tag{3}$$

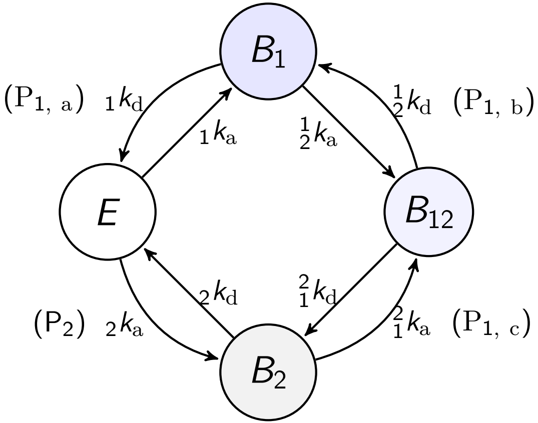
$$\frac{\partial B_{12}}{\partial t_c} = {}^1_2k_\mathrm{a}B_1C_2 + {}^2_1k_\mathrm{a}B_2C_1 - {}^1_2k_\mathrm{d}B_{12} - {}^2_1k_\mathrm{d}B_{12}, \tag{4}$$

$$\frac{\partial B_2}{\partial t_c} = {}^2_1k_\mathrm{d}B_{12} + {}_2k_\mathrm{a}(1 - B_\Sigma)C_2 - {}_2k_\mathrm{d}B_2 - {}^2_1k_\mathrm{a}B_2C_1, \tag{5}$$

$$B_\Sigma = B_1 + B_{12} + B_2 \tag{6}$$

- $1 - B_\Sigma$ empty receptor concentration
- Initially no bound ligand $B_1(x,0) = B_{12}(x,0) = B_2(x,0) = 0$,

Multiple-Component Reactions



Reaction Kinetics

- Adding these three equations we find

$$\frac{\partial B_{\Sigma}}{\partial t} = {}_1k_{\mathrm{a}}(1 - B_{\Sigma}) + {}_2k_{\mathrm{a}}(1 - B_{\Sigma}) - {}_1k_{\mathrm{d}}B_1 - {}_2k_{\mathrm{d}}B_2 \quad (7)$$

- The only change in the total ligand concentration is due to association/dissociation.

Bulk Compartment

- We can think of Pe^{-1} as a perturbation parameter and use the fact that $D \ll 1$ to arrive at the leading order equations:

$$\frac{\partial C_i}{\partial t_c} = -y(1-y)\frac{\partial C_i}{\partial x}, \tag{8}$$

$$C_i(0, y, t_c) = 1, \tag{9}$$

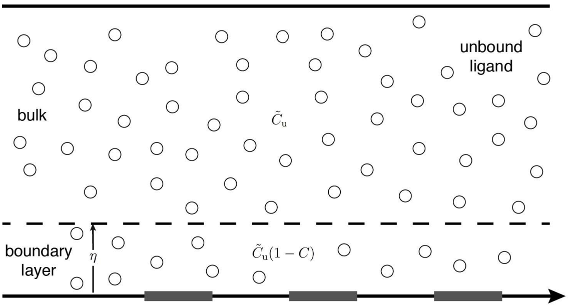
$$C_i(x, y, 0) = 0, \tag{10}$$

$$0 = \frac{\partial B_1}{\partial t_c} + \frac{\partial B_{12}}{\partial t_c}, \tag{11}$$

$$0 = \frac{\partial B_{12}}{\partial t_c} + \frac{\partial B_2}{\partial t_c}. \tag{12}$$

Two Compartment

- Compartment model



Diffusive Layers

- There may be discontinuity between the solution in the bulk compartment and the solution in the boundary layer.
- To fix this one would introduce an intermediate (*diffusive layer*) to smooth out any discontinuities.
- But the reaction dynamics do not occur *on this time scale*, so we will not concern ourselves with including such layers.

Unstirred Layer on the Reactive Time Scale

- Diffusion in the vertical direction balances with convection in the x direction.

$$D_r \frac{\partial^2 C_1}{\partial \eta^2} = \eta \frac{\partial C_1}{\partial x},$$
$$C_1(0, \eta, t) = 1.$$

- Here $\eta = \mathrm{Pe}^{1/3} y$ is the stretched layer coordinate.
- Change completely driven by reaction at the boundary.
- As we exit the layer, the concentration in the unstirred layer must match the uniform outer concentration $C(x, \infty, t) = 1$

Unstirred Layer

- Diffusive flux condition

$$D_r \frac{\partial C_1}{\partial \eta}(x, 0, t) = \mathrm{Da}\left(\frac{\partial B_1}{\partial t} + \frac{\partial B_{12}}{\partial t}\right) \qquad (13)$$

- Da is the *Damköhler Number*, and represents the ratio of reaction to diffusion.
- $\mathrm{Da} \ll 1$ for most reactions, *key perturbation parameter*.

Reaction Kinetics

- Need to get C_i in terms of B_j.

$$\frac{\partial B_1}{\partial t} = {}_1k_\mathrm{a}(1 - B_\Sigma)C_1 + {}^1_2k_\mathrm{d}B_{12} - {}_1k_\mathrm{d}B_1 - {}^1_2k_\mathrm{a}B_1C_2,$$
$$\frac{\partial B_{12}}{\partial t} = {}^1_2k_\mathrm{a}B_1C_2 + {}^2_1k_\mathrm{a}B_2C_1 - {}^1_2k_\mathrm{d}B_{12} - {}^2_1k_\mathrm{d}B_{12},$$
$$\frac{\partial B_2}{\partial t} = {}^2_1k_\mathrm{d}B_{12} + {}_2k_\mathrm{a}(1 - B_\Sigma)C_2 - {}^2_1k_\mathrm{a}B_2C_1 - {}_2k_\mathrm{d}B_2.$$

Unstirred Layer

- Consider the set of PDE's for C_1

$$D_r \frac{\partial^2 C_1}{\partial \eta^2} = \eta \frac{\partial C_1}{\partial x} \tag{14}$$

$$D_r \frac{\partial C_1}{\partial \eta}(x, 0, t) = \mathrm{Da}\left(\frac{\partial B_1}{\partial t} + \frac{\partial B_{12}}{\partial t}\right), \tag{15}$$

- Introduce a Laplace transform in x in (14) and use (15):

$$C_1(x, 0, t) = 1 - \frac{\mathrm{Da}}{D_r^{2/3} 3^{\frac{1}{3}} \Gamma(\frac{2}{3})} \int_0^x \left(\frac{\partial B_1}{\partial t} + \frac{\partial B_{12}}{\partial t}\right)(\nu, t) \frac{\mathrm{d}\nu}{(x - \nu)^{2/3}}.$$

Ligand Depletion

- Convolution integral represents upstream ligand depletion

$$C_1(x,0,t) = 1 - \frac{\mathrm{Da}}{D_r^{2/3} 3^{\frac{1}{3}} \Gamma\left(\frac{2}{3}\right)} \int_0^x \left(\frac{\partial B_1}{\partial t} + \frac{\partial B_{12}}{\partial t} \right)(\nu, t) \frac{\mathrm{d}\nu}{(x-\nu)^{2/3}}$$

- Ligand concentration a perturbation away from the outer concentration.
- Defined as

$$J^{\alpha} f(x) = \int_0^x f(\nu) \frac{\mathrm{d}\nu}{(x-\nu)^{1-\alpha}}, \qquad (16)$$

one may recognize the integral term in C_1 as a fractional integral, with $\alpha = 1/3$.

Bound State System

- The bound state system is then:

$$\begin{aligned}
\frac{\partial B_1}{\partial t} &= (1 - B_\Sigma)C_1 - {}_1K_d B_1 - {}^1_2K_a B_1 C_2 + {}^1_2K_d B_{12} \\
\frac{\partial B_{12}}{\partial t} &= {}^1_2K_a B_1 C_2 - {}^1_2K_d B_{12} + {}^2_1K_a B_2 C_1 - {}^2_1K_d B_{12} \\
\frac{\partial B_2}{\partial t} &= {}^2_1K_d B_{12} - {}^2_1K_a B_2 C_1 + {}_2K_a(1 - B_\Sigma)C_2 - {}_2K_d B_2
\end{aligned}$$

with

$$C_1(x,0,t) = 1 - \frac{\mathrm{Da}}{D_r^{2/3} 3^{\frac{1}{3}} \Gamma(\frac{2}{3})} \int_0^x \left(\frac{\partial B_1}{\partial t} + \frac{\partial B_{12}}{\partial t} \right)(\nu, t) \frac{\mathrm{d}\nu}{(x-\nu)^{2/3}}$$

$$C_2(x,0,t) = 1 - \frac{\mathrm{Da}}{3^{\frac{1}{3}} \Gamma(\frac{2}{3})} \int_0^x \left(\frac{\partial B_1}{\partial t} + \frac{\partial B_{12}}{\partial t} \right)(\nu, t) \frac{\mathrm{d}\nu}{(x-\nu)^{2/3}}$$

Perturbation Approximation

- $\mathrm{Da} \ll 1$, so we can search for a perturbation expansion of the form
$$\mathbf{B} = {}^0\mathbf{B} + \mathrm{Da}\,{}^1\mathbf{B} + O(\mathrm{Da}^2). \tag{17}$$
- Leading order:
$$\frac{\mathrm{d}\,{}^0\mathbf{B}}{\mathrm{d}t} = -A\,{}^0\mathbf{B} + \mathbf{e}_1 + {}_2K_a\mathbf{e}_3 \tag{18}$$
$${}^0\mathbf{B}(t) = (I - e^{-At})[A^{-1}(\mathbf{e}_1 + {}_2K_{\mathrm{a}}\mathbf{e}_3)], \tag{19}$$
e.g. well mixed approximation.
- The spatial dependence in ${}^1\mathbf{B}(x,t) \sim x^{1/3}$.

Perturbation Approximation

- Thus we may write

$$\mathbf{B}(x,t) = (I - e^{-At})[A^{-1}(\mathbf{e}_1 + {}_2K_\mathrm{a} + x^{1/3}\mathrm{Da}\,{}^1\mathbf{B}(t)] + O(\mathrm{Da}^2). \quad (20)$$

- Problem: ${}^1\mathbf{B}$ contains a secular term of the form $te^{-\lambda t}$ in one of its components.
- A multiple scale expansion would be unweildy, and would have to be manipulated again to obtain an expression of physical relavance.

Another Approximation

- We are really interested in $\overline{\mathbf{B}}$.
- What if we could derive a set of equations for $\overline{\mathbf{B}}$, and solve them numerically using a standard ODE Package?

Averaged Bound State System

- To do this we would integrate both sides of

$$\frac{\partial B_1}{\partial t} = (1 - B_\Sigma)C_1 - {}_1K_d B_1 - {}^1_2K_a B_1 C_2 + {}^1_2K_d B_{12}$$
$$\frac{\partial B_{12}}{\partial t} = {}^1_2K_a B_1 C_2 - {}^1_2K_d B_{12} + {}^2_1K_a B_2 C_1 - {}^2_1K_d B_{12}$$
$$\frac{\partial B_2}{\partial t} = {}^2_1K_d B_{12} - {}^2_1K_a B_2 C_1 + {}_2K_a(1 - B_\Sigma)C_2 - {}_2K_d B_2$$

using

$$C_1(x,0,t) = 1 - \frac{\mathrm{Da}}{D_r^{2/3} 3^{\frac{1}{3}} \Gamma(\frac{2}{3})} \int_0^x \left(\frac{\partial B_1}{\partial t} + \frac{\partial B_{12}}{\partial t} \right)(\nu, t) \frac{\mathrm{d}\nu}{(x-\nu)^{2/3}},$$
$$C_2(x,0,t) = 1 - \frac{\mathrm{Da}}{3^{\frac{1}{3}} \Gamma(\frac{2}{3})} \int_0^x \left(\frac{\partial B_1}{\partial t} + \frac{\partial B_{12}}{\partial t} \right)(\nu, t) \frac{\mathrm{d}\nu}{(x-\nu)^{2/3}}.$$

How to Deal With Convolution Integral

- We may exploit the fact that to leading order B is independent of space

$$C_1(x,0,t) = 1 - \frac{\mathrm{Da}}{D_r^{2/3} 3^{\frac{1}{3}} \Gamma(\frac{2}{3})} \int_0^x \left(\frac{\partial B_1}{\partial t} + \frac{\partial B_{12}}{\partial t} \right)(\nu, t) \frac{\mathrm{d}\nu}{(x-\nu)^{2/3}}$$

$$B_1(x,t) = {}^0B_1(t) + \mathrm{Da}\,{}^1B_1(x,t) + O(\mathrm{Da}^2)$$

- By substituting our expansion into C_1 we arrive at

$$C_1(x,0,t) = 1 - \frac{\mathrm{Da}}{D_r^{2/3} 3^{\frac{1}{3}} \Gamma(\frac{2}{3})} \int_0^x \left(\frac{\mathrm{d}\,{}^0B_1}{\mathrm{d}t} + \frac{\mathrm{d}\,{}^0B_{12}}{\mathrm{d}t} \right)(t) \frac{\mathrm{d}\nu}{(x-\nu)^{2/3}} + O(\mathrm{Da}^2)$$

How to Deal With Convolution Integral

- Since time dependence factors out of the integral, we may write

$$C_1(x,0,t) = 1 - \mathrm{Da}\,h(x)\left(\frac{\mathrm{d}^0 B_1}{\mathrm{d}t} + \frac{\mathrm{d}^0 B_{12}}{\mathrm{d}t}\right) + O(\mathrm{Da}^2) \quad (21)$$

where,

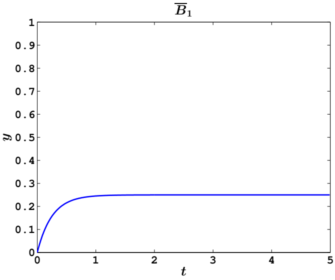
$$h(x) = \frac{1}{3^{1/3}\Gamma(2/3)}\int_0^x (x-\nu)^{-2/3}\,\mathrm{d}\nu = \frac{3^{2/3}x^{1/3}}{\Gamma(2/3)}. \quad (22)$$

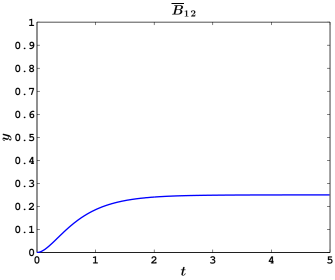
ERC Equations

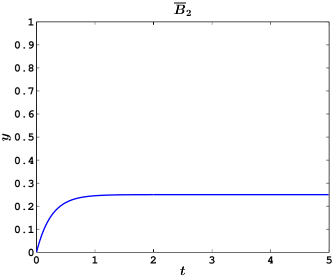
- Using these manipulations and some algebra we can derive a set of nonlinear ODE's, *Effective Rate Constant Equations* , for $\overline{\mathbf{B}}$:

$$\frac{\mathrm{d}\overline{\mathbf{B}}}{\mathrm{d}t} = (I + \mathsf{Da} N(\overline{\mathbf{B}}))^{-1}(-A\overline{\mathbf{B}} + \mathbf{e}_1 + {}_2K_{\mathrm{a}}\mathbf{e}_3) + \mathcal{O}(\mathsf{Da}^2).$$

ERC Equation Solution







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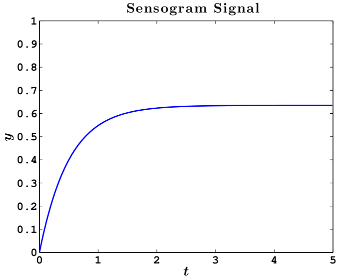


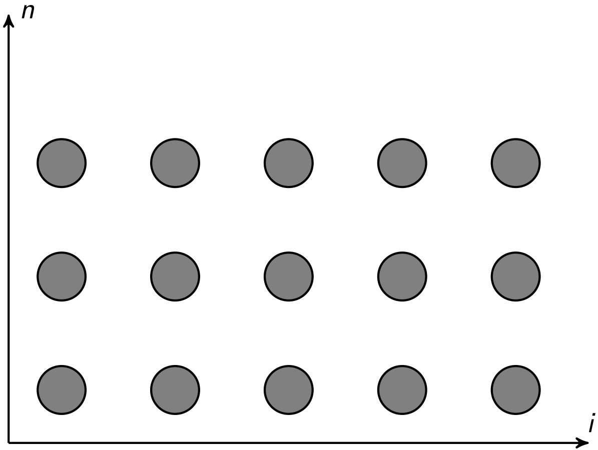
- Da $= .01$.
- Reaction rates equal to one.

Numerics

- Used a finite difference algorithm

$$\frac{\partial B^1_{i,n+1}}{\partial t} = (1 - B^{\Sigma}_{i,n}) C^1_{i,n+1} - {}_1K_d B^1_{i,n} - {}^1_2K_a B^1_{i,n} C^2_{i,n+1} + {}^1_2K_d B^{12}_{i,n},$$
$$\frac{\partial B^{12}_{i,n+1}}{\partial t} = {}^1_2K_a B^2_{i,n} C^2_{i,n+1} - {}^1_2K_d B^{12}_{i,n} + {}^2_1K_a B^2_{i,n} C^1_{i,n+1} - {}^2_1K_d B^{12}_{i,n},$$
$$\frac{\partial B^2_{i,n+1}}{\partial t} = {}^2_1K_d B^{12}_{i,n} - {}^2_1K_a B^2_{i,n} C^1_{i,n+1} + {}_2K_a(1 - B^{\Sigma}_{i,n}) C^2_{i,n+1} - {}_2K_d B^2_{i,n}.$$

Multiple-Component Reactions



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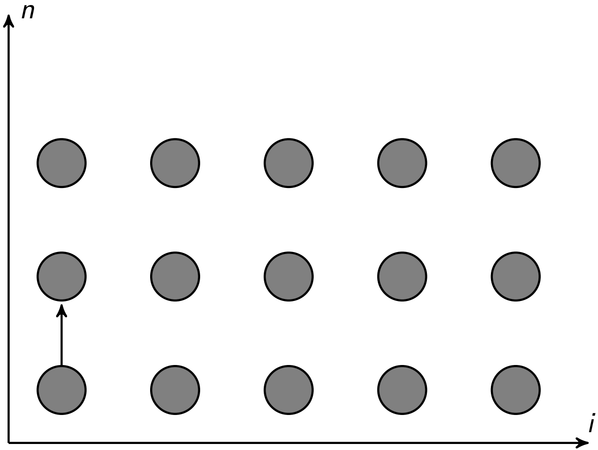

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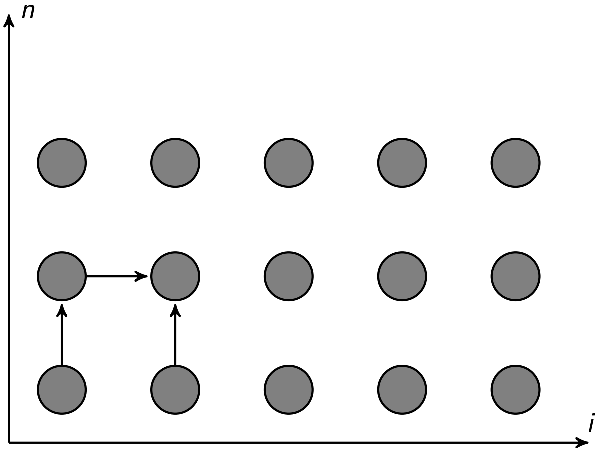

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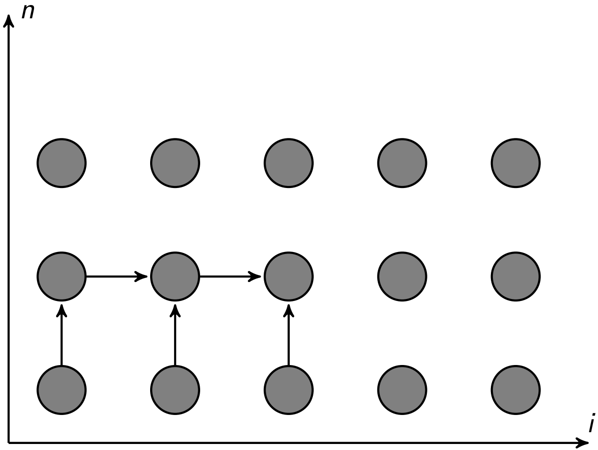

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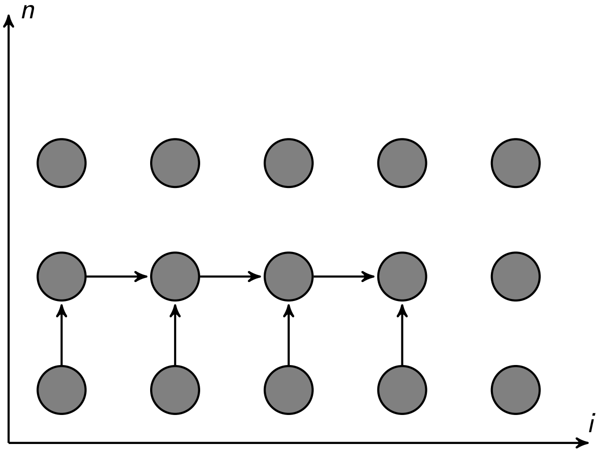

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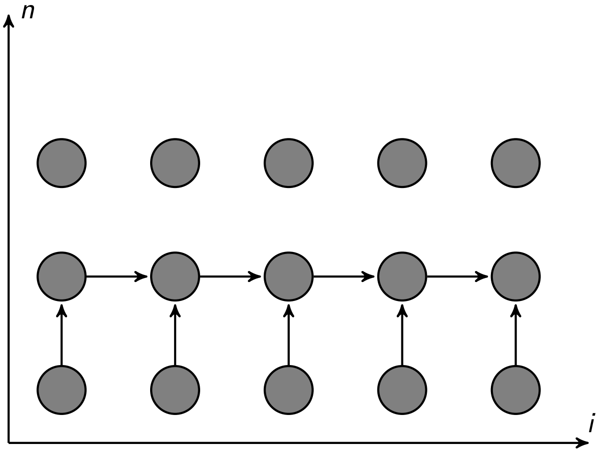

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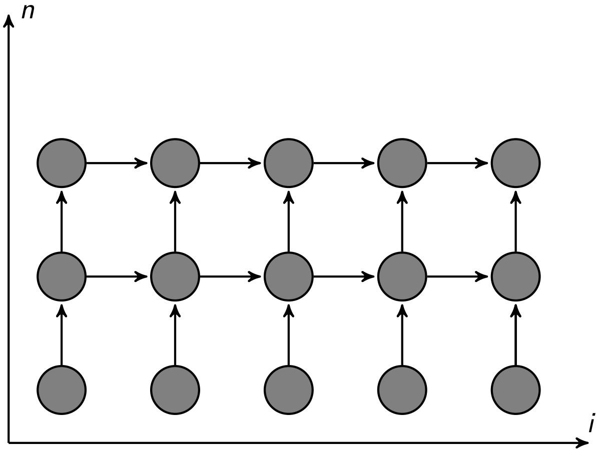


Singular Convolution Integral

- Difficult to deal with singularity

$$C^1_{i,n+1} = 1 - \frac{\mathrm{Da}}{\mathrm{D}_r^{2/3} 3^{\frac{1}{3}} \Gamma(\frac{2}{3})} \int_0^{x_i} \left(\frac{\partial B_1}{\partial t}(x_i - \xi, t_{n+1}) + \frac{\partial B_{12}}{\partial t}(x_i - \xi, t_{n+1}) \right)(\nu, t) \frac{\mathrm{d}\xi}{\xi^{-2/3}}$$

- Use trapezoidal rule to discretize the integral

Convolution Integral

- Subtract out the singularity

$$C^1_{i,n+1} = 1 - \frac{\mathrm{Da}}{\mathrm{D}_r^{2/3} 3^{\frac{1}{3}} \Gamma\left(\frac{2}{3}\right)} \left[\int_0^{x_i} \left(\frac{\partial B_1}{\partial t}(x_i - \xi, t_{n+1}) - \frac{\partial B^1_{i,n+1}}{\partial t} + \frac{\partial B_{12}}{\partial t}(x_i - \xi, t_{n+1}) - \frac{\partial B^{12}_{i,n+1}}{\partial t} \frac{\mathrm{d}\xi}{\xi^{-2/3}} \right) + 3x_i^{\frac{1}{3}} \left(\frac{\partial B^1_{i,n+1}}{\partial t} + \frac{\partial B^{12}_{i,n+1}}{\partial t} \right) \right]$$

- Even when singularity is subtracted out, convergence is only $O(\Delta x^{2/3})$ due to functional form.
- Temporal convergence $O(\Delta t^2)$, from AB2 time-stepping scheme.

Results

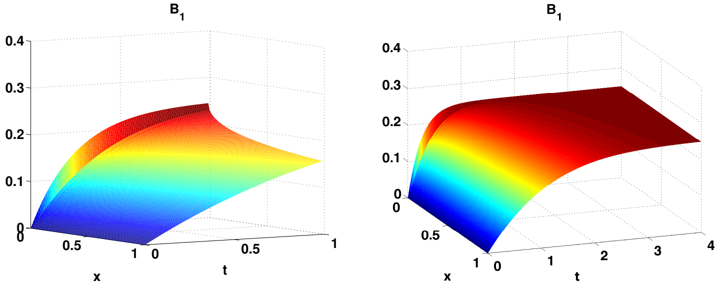
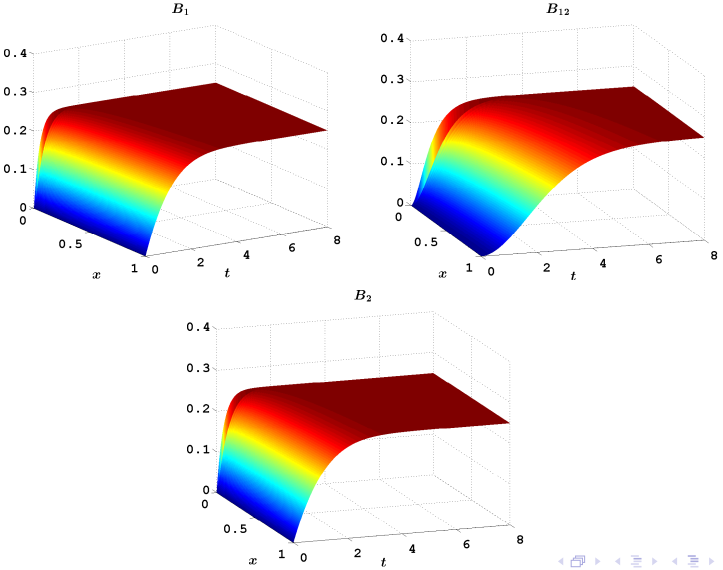


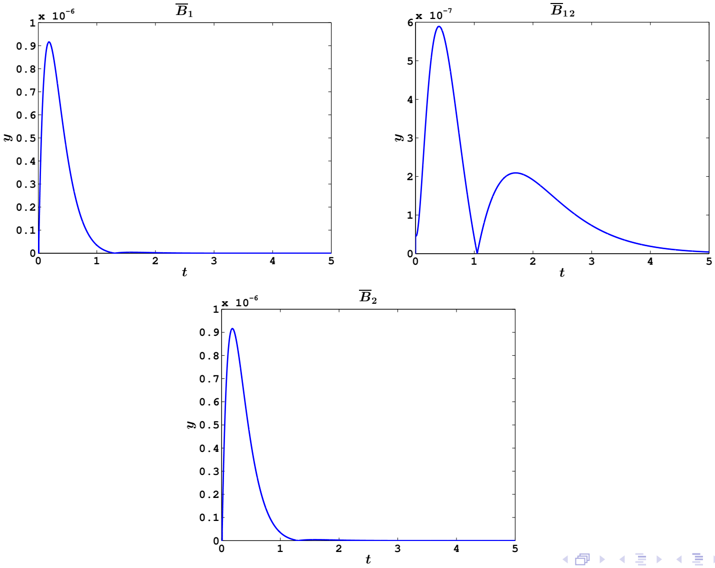
Figure : Left: B_1 after 1 second. Right: B_1 after 5 seconds

- $\mathrm{Da} = 2$.
- All reaction rate constants taken to be 1

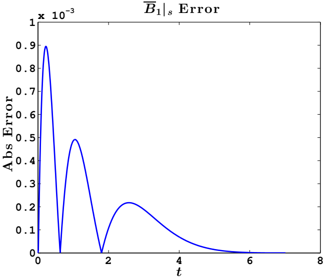
Results

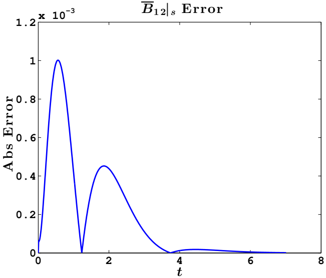


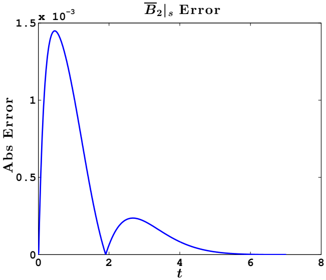
Error in ERC Equations



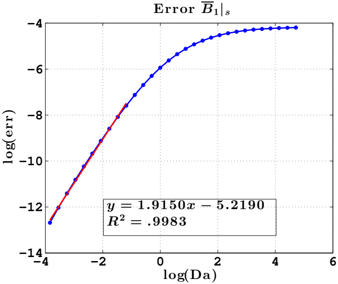
Error in ERC Equations

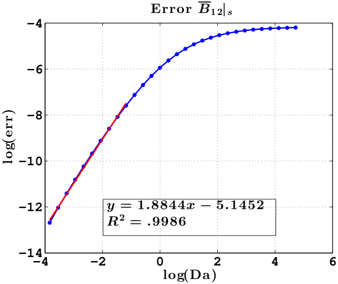


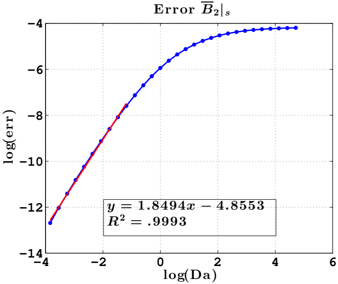




ERC Error vs Da







Wash Phase

- We have derived similar results for the wash phase.
- Recall in the wash phase, only the buffer fluid is flowing through the biosensor.

Wash Phase

- In this case, we still have the same kinetics system at the boundary,

$$\frac{\partial B_1}{\partial t} = (1 - B_\Sigma)C_1 - {}_1K_d B_1 - {}^1_2K_a B_1 C_2 + {}^1_2K_d B_{12},$$
$$\frac{\partial B_{12}}{\partial t} = {}^1_2K_a B_1 C_2 - {}^1_2K_d B_{12} + {}^2_1K_a B_2 C_1 - {}^2_1K_d B_{12},$$
$$\frac{\partial B_2}{\partial t} = {}^2_1K_d B_{12} - {}^2_1K_a B_2 C_1 + {}_2K_a(1 - B_\Sigma)C_2 - {}_2K_d B_2.$$

- Unbound ligand concentration at the surface will be different, *i.e.* only trace amounts.

Wash Phase

- Therefore instead of

$$C_1(x,0,t) = 1 - \frac{\mathrm{Da}}{D_r^{2/3} 3^{\frac{1}{3}} \Gamma(\frac{2}{3})} \int_0^x \left(\frac{\partial B_1}{\partial t} + \frac{\partial B_{12}}{\partial t} \right)(\nu, t) \frac{\mathrm{d}\nu}{(x-\nu)^{2/3}},$$

we have

$$C_1(x,0,t) = - \frac{\mathrm{Da}}{D_r^{2/3} 3^{\frac{1}{3}} \Gamma(\frac{2}{3})} \int_0^x \left(\frac{\partial B_1}{\partial t} + \frac{\partial B_{12}}{\partial t} \right)(\nu, t) \frac{\mathrm{d}\nu}{(x-\nu)^{2/3}},$$

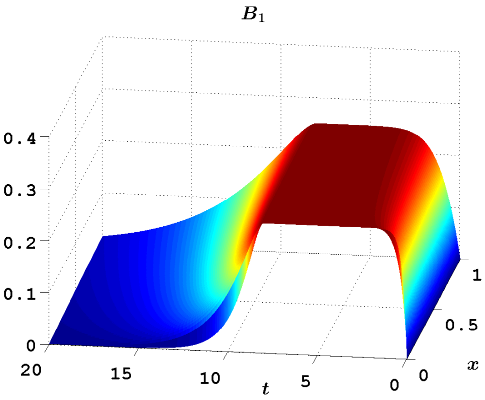
- In this case $\frac{\partial B_i}{\partial t} < 0$, and $C_1 = O(\mathrm{Da})$.

Wash Phase Results

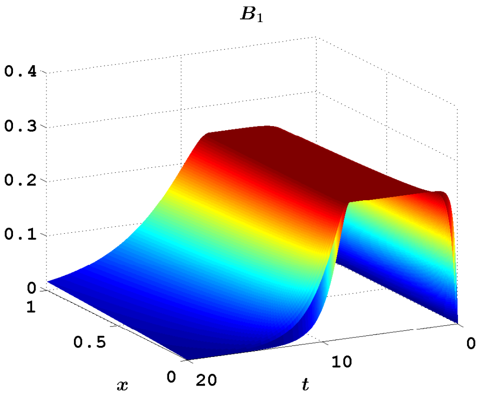
- ERC equations in this case are

$$\frac{\mathrm{d}\overline{\mathbf{B}}}{\mathrm{d}t} = (I + \mathrm{Da}N(\overline{\mathbf{B}}))^{-1}(-D\overline{\mathbf{B}}) + O(\mathrm{Da}^2) \qquad (23)$$

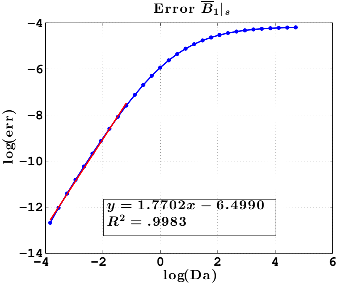
Wash Phase Results: FD Solution

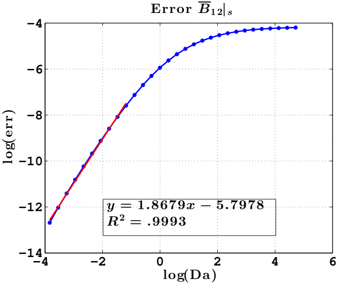


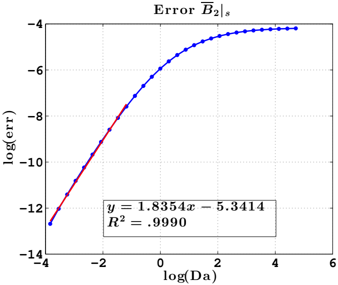
Wash Phase Results: FD Solution



Wash Phase Results: ERC Error vs. Da







Recovering Reaction Rates

- Overall Goal: What are the reaction rates?
  - Can we actually find cases where **different rate constants give the same signal**?
  - Can we develop a curve fitting algorithm?

Recovering Reaction Rates

- Take Da $= 0$ and study the linear set of ODE's

$$\frac{\mathrm{d}\mathbf{B}}{\mathrm{d}t} = -A\mathbf{B} + \mathbf{f}, \qquad \mathbf{B}(0) = \mathbf{0}. \tag{24}$$

- Use (24) as our data.

Recovering Reaction Rates

- Here

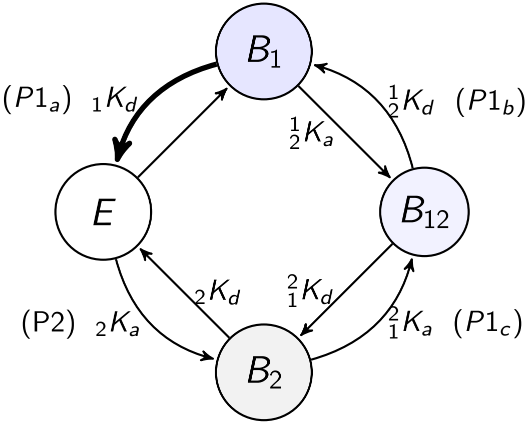
$$A = \begin{pmatrix} (1 + {}_1K_d + {}^1_2K_a) & 1 - {}^1_2K_d & 1 \\ -{}^1_2K_a & ({}^1_2K_d + {}^2_1K_d) & -{}^2_1K_a \\ {}_2K_a & {}_2K_a - {}^2_1K_d & ({}_2K_a + {}_2K_d + {}^2_1K_a) \end{pmatrix}$$

and $\mathbf{f} = \mathbf{e}_1$ or $\mathbf{f} = {}_2K_{\mathrm{a}}\mathbf{e}_3$

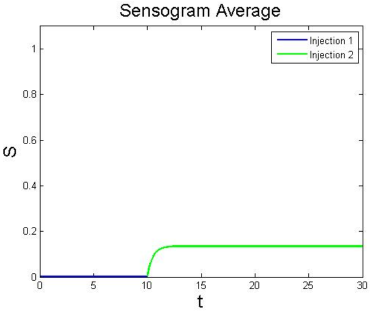
Methodology

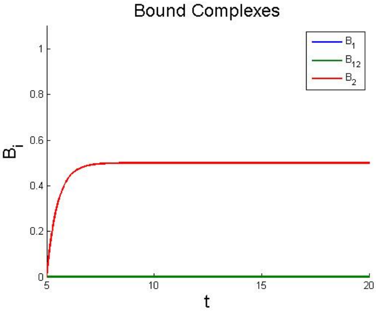
- First inject ligand one until the system reaches an equilibrium, then inject ligand two.
- Broke the problem up into cases based on the size of ${}_1K_{\mathrm{d}},\ {}_2K_{\mathrm{a}},\ {}_2K_{\mathrm{d}}$.

Recovering Reaction Rates



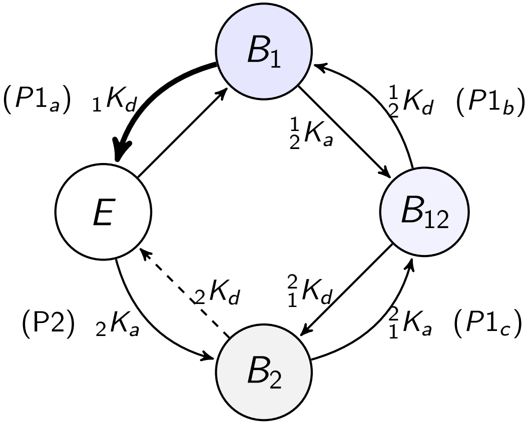
Recovering Reaction Rates



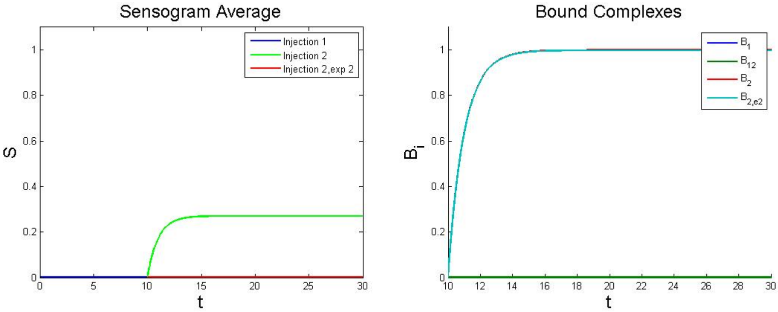


- ${}_1K_{\mathrm{d}} = 100$

Recovering Reaction Rates

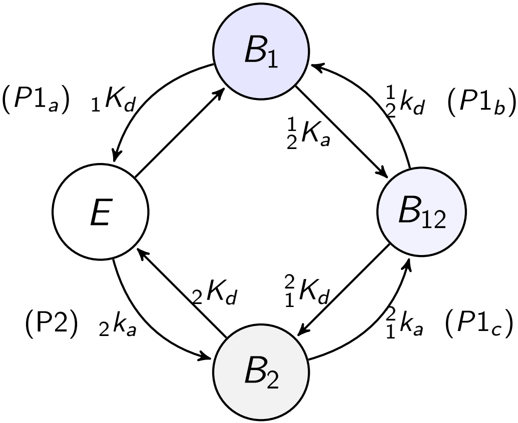


Recovering Reaction Rates

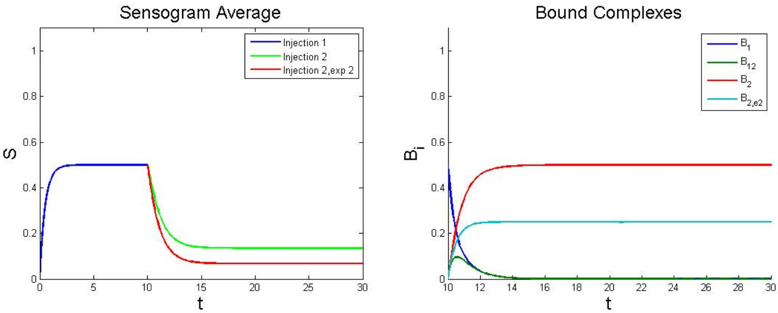


- ${}_1K_d = 100, \ {}_2K_d = \frac{1}{100}$

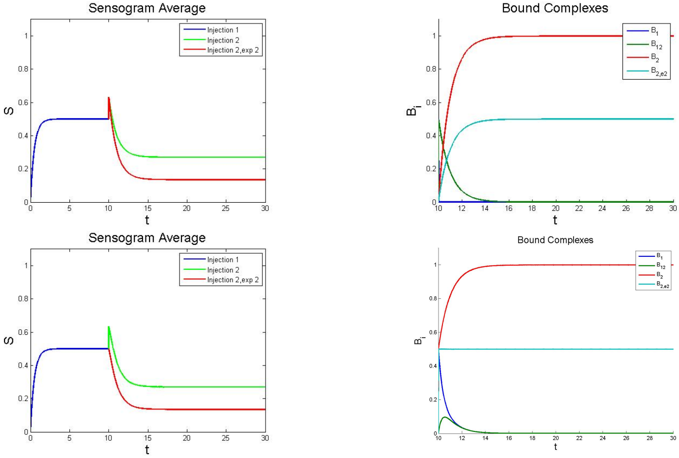
Recovering Reaction Rates



Recovering Reaction Rates

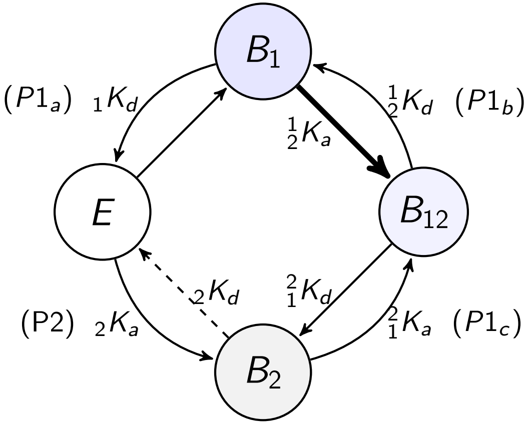


Ambiguous Sensogram

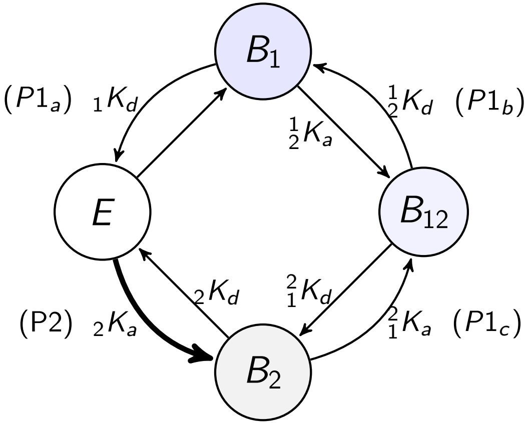


- Left: ${}_2K_d = 100$, ${}^1_2K_a = \frac{1}{100}$. Right: ${}_2K_a = 100$. Both: $C_1 = 1$.

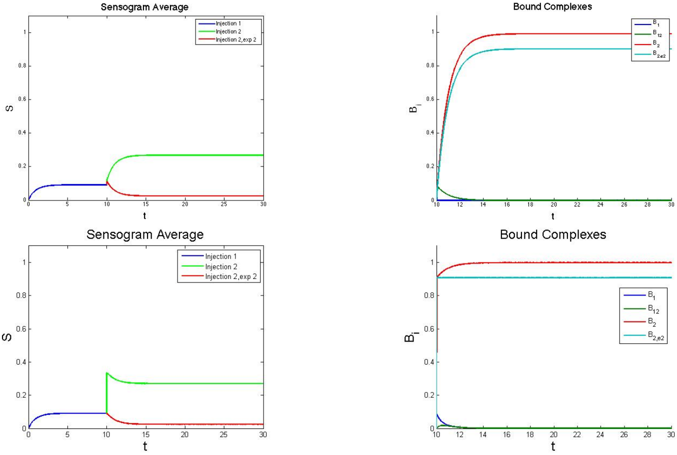
Ambiguous Sensogram: Case 1



Ambiguous Sensogram: Case 2



Clarified Sensogram



- Left: ${}_2K_d = \frac{1}{100}$, ${}_2^1K_a = 100$. Right: ${}_2K_a = 100$. Both: $C_1 = .1$.

Single Ligand Analysis

- When studying the single ligand process, there is only one type of reaction at the boundary.
- In this case the reacting species concentration obeys they equation

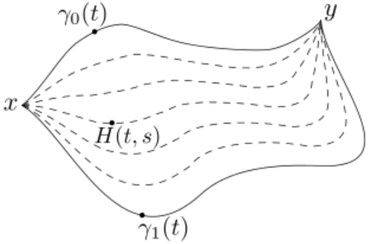
$$\frac{\partial B}{\partial t} = (1 - B)\left(1 - \frac{\mathrm{Da}}{3^{1/3}\Gamma(2/3)} \int_0^x \frac{\partial B}{\partial t}(\nu, t) \frac{\mathrm{d}\nu}{(x-\nu)^{2/3}}\right) - KB$$

- Can we find an analytic expression for B or $\overline{B}$ when $\mathrm{Da} = O(1)$?

A Homotopy Method

- *Homotopy*: a continuous deformation of one curve into another.

$$\mathcal{H}(t,s) = (1-s)\gamma_0(t) + s\gamma_1(t), \qquad s \in [0,1]$$



- Can we try the same thing with differential operators?

A Homotopy of Differential Operators

- Many differential operators $\mathcal{A}$ can be composed into a linear part $\mathcal{L}$, and nonlinear part $\mathcal{N}$

$$\underbrace{\mathcal{L}(B) + \mathcal{N}(B)}_{\mathcal{A}(B)} = \mathcal{F}. \tag{25}$$

- We can draw a homotopy between $\mathcal{L}$ and $\mathcal{A}$

$$\mathcal{H}(B, p) = (1 - p)\mathcal{L}(B) + p\mathcal{A}(B), \qquad p \in [0, 1]. \tag{26}$$

Nuts and Bolts

- Therefore we can propose a series solution to

$$\begin{aligned} &\mathcal{H}(B,p) = 1 \\ \Leftrightarrow &(1-p)\mathcal{L}(B) + p\mathcal{A}(B) = \mathcal{F}, \qquad p \in [0,1]. \end{aligned}$$

of the form

$$B(x,t) = B_0(x,t) + pB_1(x,t) + p^2 B_2(x,t) + \cdots.$$

Nuts and Bolts

- Thus when examing the p^{th} coefficient of our series in the equation

$$\Leftrightarrow (1-p)\mathcal{L}(B) + p\mathcal{A}(B) = \mathcal{F}, \qquad p \in [0,1]. \tag{27}$$

we will find that the nonlinearity is higher order.

- That is we will have an equation of the form

$$\mathcal{L}(B_i) = -\mathcal{N}(B_1, \ldots, B_{i-1}). \tag{28}$$

Single Ligand Analysis

- The equation governing the bound state in the single ligand case is

$$\frac{\partial B}{\partial t} = (1 - B)\left(1 - \frac{\mathrm{Da}}{3^{1/3}\Gamma(2/3)}\int_0^x \frac{\partial B}{\partial t}(\nu, t)\frac{\mathrm{d}\nu}{(x-\nu)^{2/3}}\right) - KB$$

- First we obtain an expression for $\overline{B}$ by averaging each side, and rearranging some terms:

$$\underbrace{\frac{\mathrm{d}\overline{B}}{\mathrm{d}t} + (1+K)\overline{B}}_{\mathcal{L}} + \underbrace{\frac{\mathrm{Da}}{3^{1/3}\Gamma(2/3)}\overline{(B-1)\int_0^x \frac{\partial B}{\partial t}(\nu, t)\frac{\mathrm{d}\nu}{(x-\nu)^{-2/3}}}}_{\mathcal{N}} = 1$$

Series Solution

- Propose and substitute a series solution.

$$B(x,t) = B_0(x,t) + pB_1(x,t) + p^2 B_{12}(x,t) + \cdots \tag{29}$$
$$\mathcal{H}(B,p) = 1. \tag{30}$$

- Get linear ODE's for $\overline{B}_0(t)$, $\overline{B}_1(t)$, $\overline{B}_2(t), \ldots$
- An approximation to $\overline{B}$ is then given by

$$\overline{B}(t) = \overline{B}_0 + \overline{B}_1(t) + \overline{B}(t) + \cdots$$

Two Terms

- Doing this the first two terms are:

$$B_0(t) = \alpha^{-1}(1 - e^{-\alpha t})$$

$$B_1(t) = -\frac{\mathrm{Da}\bar{h}e^{-2t\alpha}(-1 + e^{t\alpha} - e^{t\alpha}t\alpha + e^{t\alpha}t\alpha^2)}{\alpha^2}$$

$$\alpha = (K + 1)$$

$$\bar{h} = \frac{\overline{x^{1/3}}}{3^{1/3}\Gamma(2/3)}$$

Issues

- Convergence of our series.
  - When $\text{Da} = O(1)$ or $\text{Da} \gg 1$, what guaruntees that our series will converge?
- Secular term of the form $te^{-\alpha t}$
  - This is not bad enough make our series converge, but still throws off the accuracy.

Convergence

- A standard technique is to embed a convergence control paramter q into our homotopy

$$(1-p)(\mathcal{L}(\overline{B})-\mathcal{L}(b_0))+qp\mathcal{A}(B)=1, \qquad p\in[0,1]. \tag{31}$$

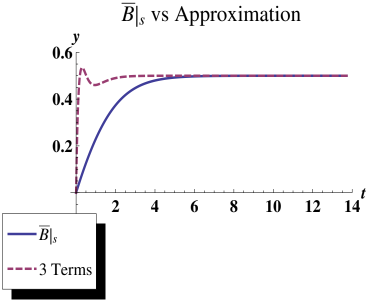
- Choose q that minimizes

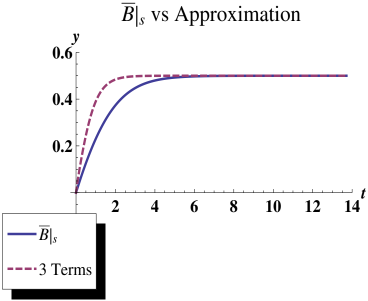
$$||\mathcal{A}(B)-1||_2^2 \tag{32}$$

- Done numerically in Mathematica.

Time Scale

- We can fix convergence, but the *time scale* is still off.





- Da $=3$; This is a 3 term approximation with and without the convergence parameter q

Time Scale

- The propose a strained time scale of the form:

$$\tau = (1 + p\omega_1 + p^2\omega_2 + \cdots)t, \qquad (33)$$

where the ω_i are choosen to eliminate secular terms.

Expansion

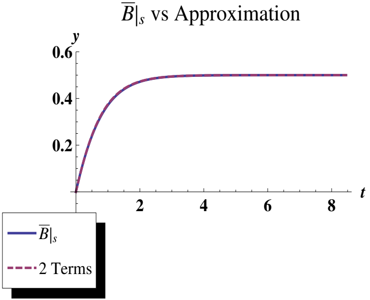
- The first two terms are:

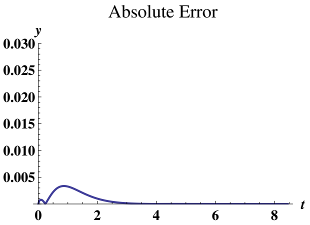
$$\overline{B}_0(\tau) = \alpha^{-1}(1 - e^{-\alpha\tau}),$$
$$\overline{B}_1(\tau; q) = \frac{q\mathrm{Da}\overline{h}e^{-2\alpha\tau}(e^{\alpha\tau} - 1)}{\alpha^2},$$
$$\tau = (1 + \omega_1 + \omega_2 + \cdots)t,$$

where $\alpha = (1 + K)$, and

$$\omega_1 = -q\mathrm{Da}\overline{h}(1 - \alpha^{-1}),$$
$$\omega_2 = \mathrm{Da}\overline{h}q\alpha^{-2}(\alpha - 1)(-\mathrm{Da}\overline{h}q + \alpha - q\alpha + \mathrm{Da}\overline{h}q\alpha),$$
$$\overline{h} = \frac{\overline{x^{1/3}}}{3^{1/3}\Gamma(2/3)}.$$

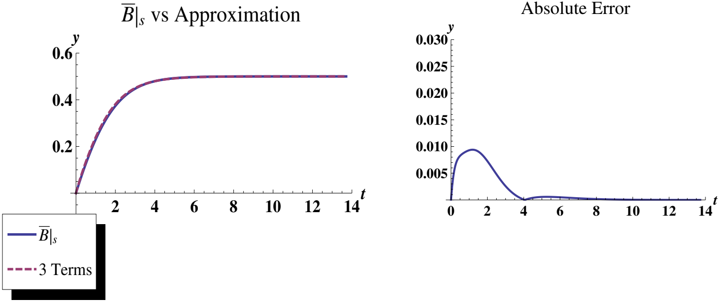
Two Term Expansion, Da $= 1/2$





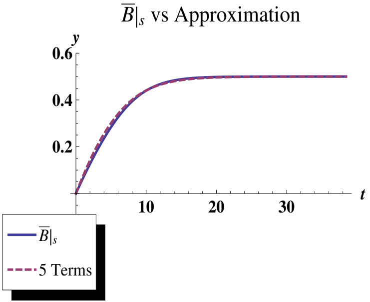
- Two term expansion, Da $= 1/2$.

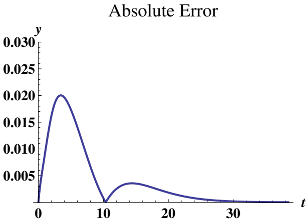
Three Term Expansion, Da = 2



- Three term Approximation, Da = 2.

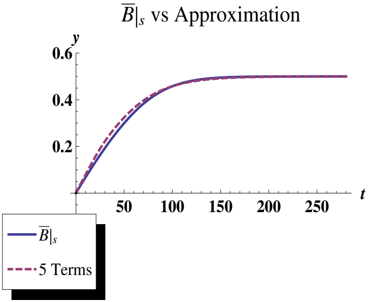
Five Term Expansion, Da = 10

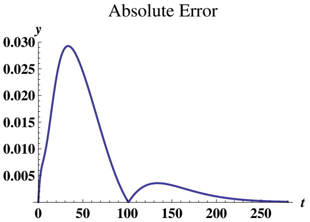




- Five term expansion, Da = 10.

Five Term Expansion, Da $= 100$





- Five term expansion, Da $= 100$.

Dissociation Phase

- The expansion in the dissociation phase is:

$$B_0(t) = \frac{e^{-k\tau}}{\alpha},$$

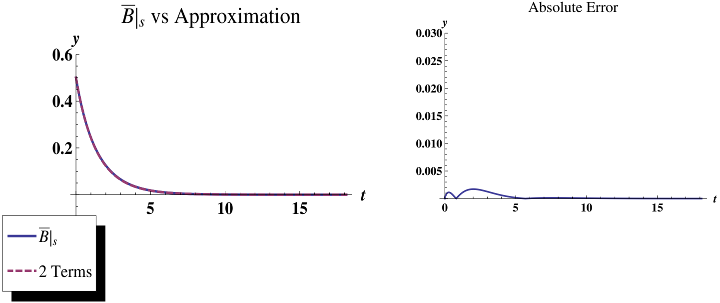
$$B_1(t) = -\frac{\mathrm{Da} e^{-2k\tau}\left(-1 + e^{k\tau}\right)\overline{h}q}{\alpha^2}$$

$$\tau = (1 + \omega_1 + \omega_2 + \cdots)t$$

$$\omega_1 = -\mathrm{Da}\overline{h}q,$$

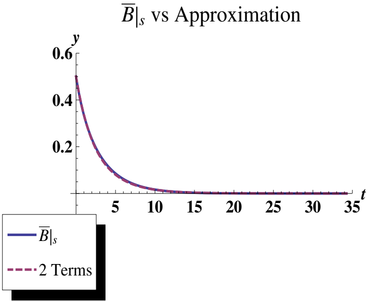
$$\omega_2 = \mathrm{Da}\overline{h}q(-1 + q + \mathrm{Da}\overline{h}q).$$

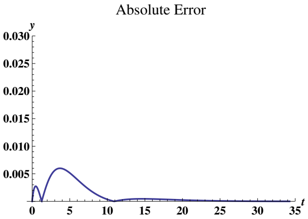
Two Term Expansion, Da $= 1/2$



- Two term expansion, Da $= 1/2$.

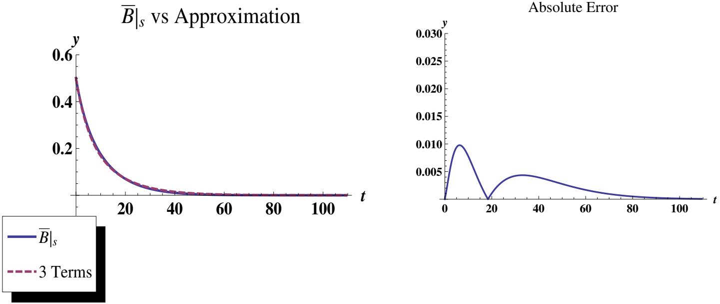
Three Term Expansion, Da $= 2$





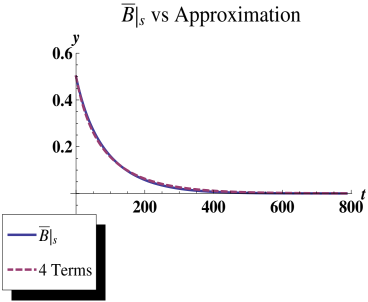
- Three term Approximation, Da $= 2$.

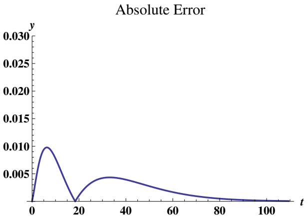
Five Term Expansion, Da = 10



- Five term expansion, Da = 10.

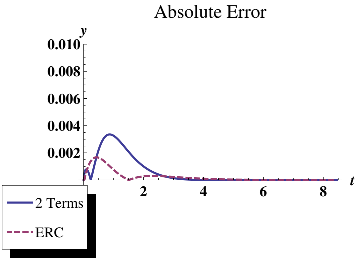
Five Term Expansion, Da = 100

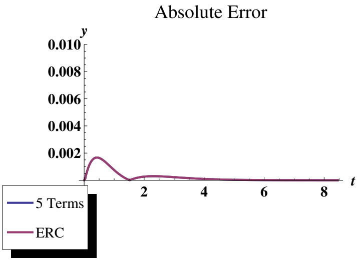




- Five term expansion, Da = 100.

Matches Up With ERC Approximation





- Left: Two term approximation vs ERC Approximation. Right: Five-Term approximation vs ERC Approximation.

Conclusions

- Modeling Multiple-Components in Optical Biosensors.
  - We must consider transport.
  - Full model simplifes to a coupled system of integrodiffential equations.
  - These equations further reduce to a set of nonlinear ODE's.
  - Formally holds for Da $\ll 1$, numerically everywhere.
- Sensogram Issues
  - Multiple reacting species make interpreting Sensogram data difficult.
  - Can fix this in certain cases by varying of C_1.

Conclusions

- Single-Component Reactions
  - Strongly nonlinear problem when $\mathrm{Da} = O(1)$.
  - Can find analytic approximations to $\overline{B}$ by applying a homotopy method.
  - Must used a strained time scale.
  - Matches up with ERC approximations.

Future Work

- Tie together multiple-receptor and multiple-ligand model.
- Nonuniform initial receptor concentration.
- Helical geometries.

References

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The End

Thanks for Coming! Questions?