

**Surface
Reaction Near
a Stagnation
Point**

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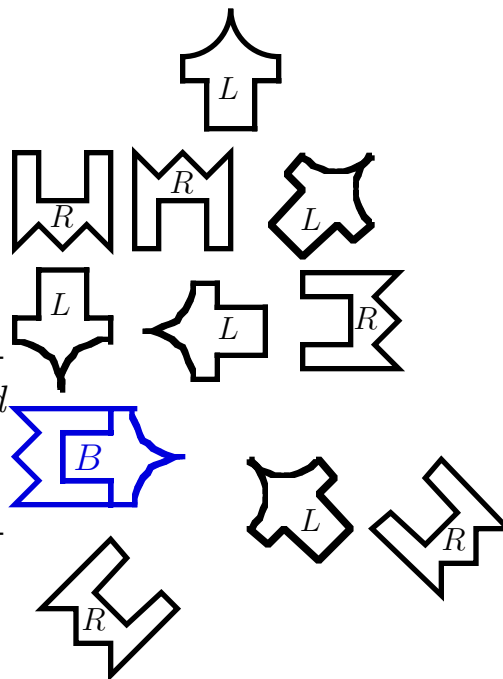
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Support provided by

University of Delaware Research Foundation

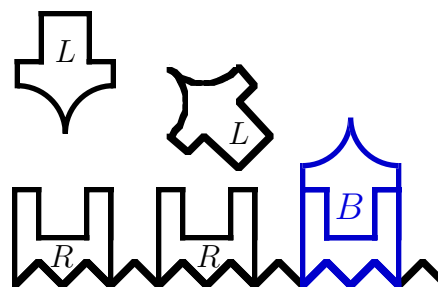
Chemical Reactions

- two reactants, L and R
- reactants float free in solution
- when reactants come together in appropriate way, reaction occurs and *bound state* B forms
- reactants can join in a variety of configurations

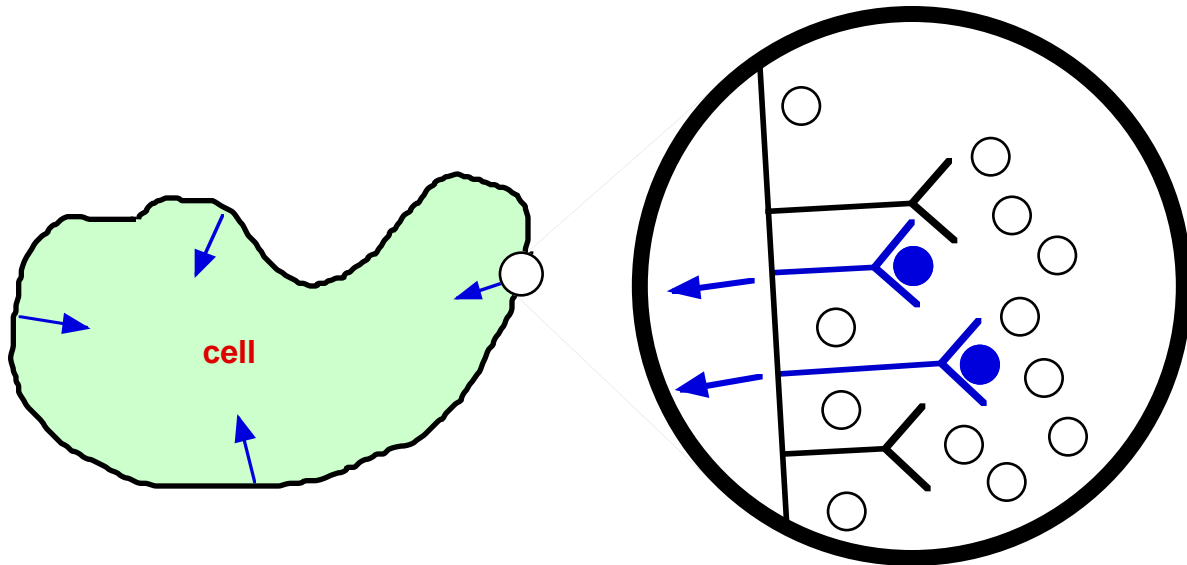


Surface-Volume Chemical Reactions

- one reactant, the *receptor* R , is attached to a two-dimensional surface
- the other reactant, the *ligand* or *analyte* L , may not be able to be attached (restricts reaction)
- reaction configurations greatly reduced



Application: Biochemical Reactions



- signals (instructions) are sent to the interior *via* receptor using ligand in exterior [1]

Rebinding

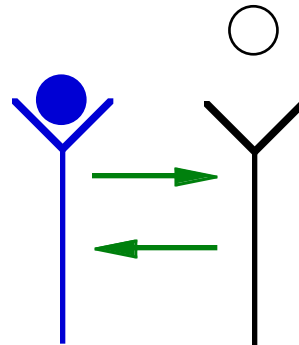
- analyte in solution (there previously or as a result of dissociation) can bind to empty receptor site (there previously or as a result of dissociation)
- ✓ simplest model: linear dependence:

$$\frac{d\tilde{B}}{d\tilde{t}} = -\tilde{k}_{\text{off}}\tilde{B} + \tilde{k}_{\text{on}}\tilde{C}(R_T - \tilde{B}), \quad (1)$$

- \tilde{C} is the concentration of free-floating ligand
- \tilde{k}_{on} is the *association rate constant*
- \tilde{k}_{off} is the *dissociation rate constant*
- R_T is the total number of receptor sites

- ✓ second term says association proportional to product of free analyte (\tilde{C}) and empty sites ($R_T - \tilde{B}$)

- ✗ How do we measure \tilde{k}_{on} and \tilde{k}_{off} ?

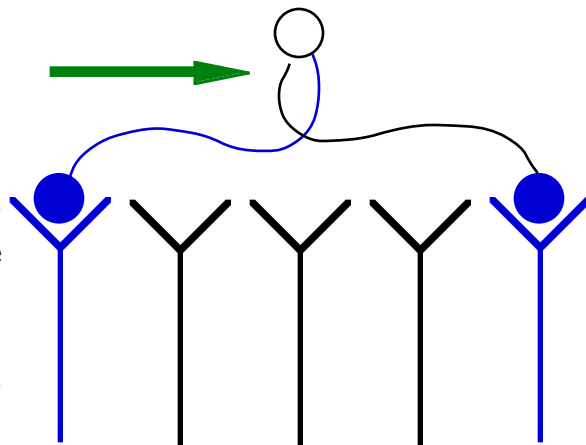


Measurement Issues

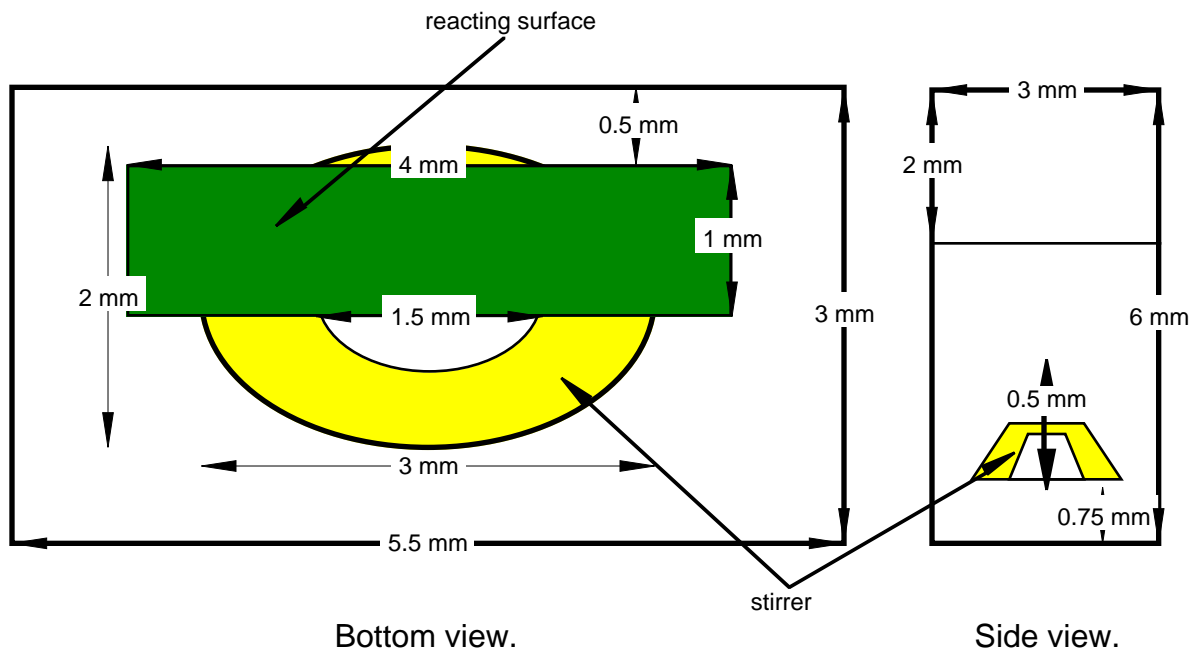
- ✓ plot \tilde{B} vs. \tilde{t} and use a nonlinear fitting program with solutions of ODE
- ✓ use an approximate difference to plot $d\tilde{B}/d\tilde{t}$ vs. \tilde{B} and use a linear fitting program with ODE (Scatchard plot)
- ✗ in both cases, something must be known (or assumed) about \tilde{C}
- how do we obtain data?
- for both of the above methods, we must measure without disturbing system (removing or disturbing analyte, etc.)

Transport Effects

- in presence of imposed flow, analyte can bind to a *different* site downstream
- ✗ functions no longer spatially independent
- ✗ equipment measures only *averages* of \tilde{B}



The IAsys



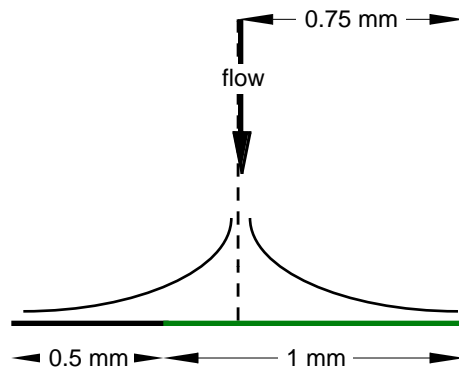
- one reactant (the analyte) is placed in solution in the well, shown at right
- solution level is roughly 2 mm below the top of the well
- volume of fluid considered is between 50 and 200 μL
- the other reactant (the receptor) is embedded in a sensor surface at the bottom of the well (green)
- solution agitated using a vibrostirrer which has an elliptical annular cross-section (yellow)
- center elliptical hole is 1 mm in the short direction
- stirrer oscillates at 140 cycles/sec in the direction shown at up to 0.5 mm amplitude (usually set at around 85% of maximum)
- polarized light beam reflects off the sensor surface and passes to a detector
- ✓ refractive changes due to the binding of the reactants are then averaged over the sensor surface to provide real-time measurement of the bound-state concentration (no disturbance!)

Simplified Flow Model

- flow is governed by convection-diffusion reaction

$$\frac{\partial \tilde{C}}{\partial \tilde{t}} = \tilde{D} \nabla^2 \tilde{C} - \tilde{\mathbf{v}} \cdot \nabla \tilde{C}$$

- ✓ Re for the system is around 300 (laminar flow)
 - sensor averages data over entire sensor surface (long compared to width)
- ✓ reduce to two-dimensional slice
 - reduce to stagnation point flow
 - ✗ severe simplification
- ✓ most of sensor surface is in neighborhood of stagnation point



$$\tilde{x} = Lx, \quad \tilde{y} = Hy_p, \quad \tilde{u}_{\tilde{y}}(\tilde{x}, \tilde{y}) = Vu_y(x, y_p)$$

- L is distance from stirrer to centerline
- H is height of stirrer
- V is maximum velocity of stirrer

Solving for the Flow

- inviscid region: stagnation point flow

$$u_x = x, \quad u_y = -y_p$$

- viscous region: *Falkner-Skan* flow

$$\begin{aligned} v_x &= x f'(y_v), & y_v &= \text{Re}^{1/2} y_p, \\ v_y &= -f(y_v), & u_x(x, y_p) &= v_x(x, y_v), \\ f''' - (f')^2 + f f'' + 1 &= 0; & f(0) &= f'(0) = 0, \quad f'(\infty) = 1 \end{aligned}$$

- ✗ transport occurs in even thinner region, so need small- y_v expansions:

$$f'(y_v) \sim 2F y_v, \quad f(y_v) = F y_v^2, \quad y_v \rightarrow 0, \quad F \approx 0.616$$

Reaction Scalings

$$y = \text{Sc}^{1/3} y_v, \quad \text{Sc} = \frac{\nu}{\tilde{D}} = \frac{\text{viscous effects}}{\text{diffusive effects}} \gg 1, \quad t = \tilde{k}_{\text{on}} C_T \tilde{t}$$

- ✓ t is reaction time scale
- C_T is initial concentration of analyte

$$C(x, y, t) = 1 - \text{Da} C_{\Delta}(x, y, t).$$

- C_{Δ} measures the disturbance in the concentration field due to the surface flux, which is proportional to Da

$$\text{Da} = \frac{\tilde{k}_{\text{on}} R_T \nu^{1/6} H^{1/2}}{V^{1/2} \tilde{D}^{2/3}} = \frac{\text{reaction "velocity"}}{\text{diffusion "velocity" in unstirred layer}}$$

- Da is the *Damköhler number*
- ✓ Da $\rightarrow 0$ (slow reaction) implies that reaction is causing very little drain on the flux, and hence transport to the surface can keep up (well-mixed limit)
- ✓ for faster reactions or slower diffusion processes, Da increases and the effects of transport must be considered

Reduced Equations

- transport equation

$$\frac{\partial^2 C_\Delta}{\partial y^2} = 2Fxy \frac{\partial C_\Delta}{\partial x} - Fy^2 \frac{\partial C_\Delta}{\partial y}$$

- flux into binding surface forms bound complex

$$\frac{\partial C_\Delta}{\partial y}(x, 0, t) = -\frac{\partial B}{\partial t}$$

- mass action law

$$\frac{\partial B}{\partial t} = (1 - B)[1 - \text{Da}C_\Delta(x, 0, t)] - KB, \quad K = \frac{\tilde{k}_{\text{off}}}{\tilde{k}_{\text{on}}C_T}$$

- initial condition

$$B(x, 0) = B_i(x)$$

- symmetry about center line

$$\frac{\partial C_\Delta}{\partial x}(0, y, t) = 0$$

- far field condition

$$C_\Delta(x, \infty, t) = 0$$

- ✗ neglecting depletion effects in finite well (okay if C_T is large)

Uniform Initial Condition

- ✓ if B_i is independent of x , then C and B are independent of x for all time

$$C_{\Delta}(x, y, t) = \frac{dB}{dt}(t)C_1(y)$$

$$\frac{d^2C_1}{dy^2} = -Fy^2 \frac{dC_1}{dy}, \quad C_1(\infty) = 0, \quad \frac{dC_1}{dy}(0) = -1,$$

$$C_1(y) = \frac{1}{3^{2/3}F^{1/3}}\Gamma\left(\frac{1}{3}, \frac{Fy^3}{3}\right)$$

Effective Rate Constants

$$\frac{dB}{dt} = \frac{1 - \alpha B}{1 + \text{Da}(1 - B)C_1(0)}, \quad \alpha = 1 + K.$$

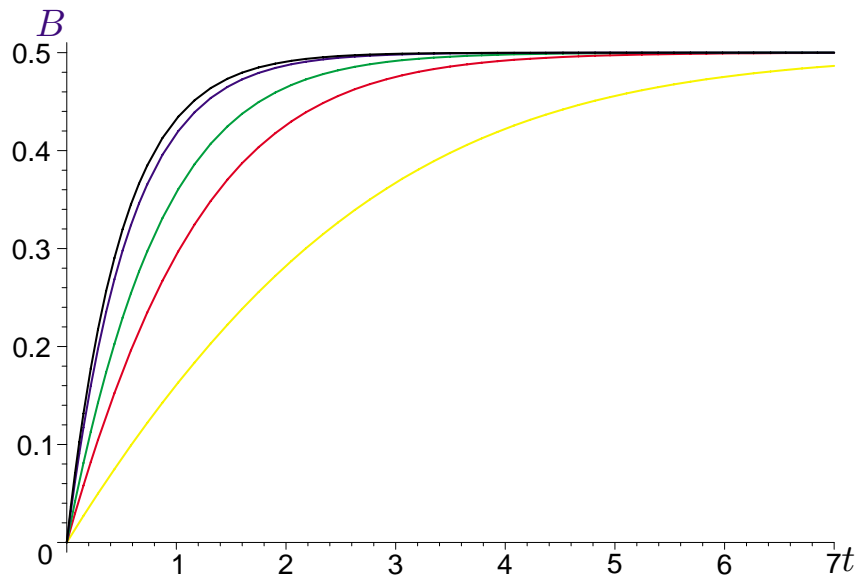
- ✓ simple, exact equation for B
- ✓ if $\text{Da} = 0$, reduces to well-mixed case
- ✓ simple interpretation: rate constant (here K) reduced by effects of transport (proportional to Da)
- ✓ data can be fit to ODE model using standard software
- ✓ denominator can be interpreted in terms of probability of dissociation/rebinding [3]

- Final solution:

$$\frac{dB}{dt} = \frac{1 - \alpha B}{1 + \gamma(1 - B)}, \quad \gamma = \frac{\text{Da}\Gamma(1/3)}{3^{2/3}F^{1/3}}$$

- ✓ can be solved implicitly
- ✗ function of stagnation flow; not generic
- exactly enough new ligand is being brought to the surface by the convective stream to replace any taken away during the reaction

Results



B versus t for $K = 1$ and $B_i = 0$. In decreasing order of thickness: $Da = 0$, 0.1, 0., 1, 3.

- ✓ as Da increases, time to equilibrium increases (slower transport limits reaction)

Nonuniform Initial Data, Small Da

$$B(x, t) \sim B_0(x, t) + \text{Da}B_1(x, t)$$

$$\frac{\partial B_0}{\partial t} = 1 - \alpha B_0, \quad B_0(x, 0) = B_i(x),$$

$$B_0(x, t) = \frac{1 - e^{-\alpha t}}{\alpha} + B_i(x)e^{-\alpha t}$$

- ✓ leading-order is well-mixed case (corresponds to $\text{Da} = 0$)

$$\frac{\partial C_\Delta}{\partial y}(\xi, 0, t) = -e^{-\alpha t} [1 - \alpha B_i(x)]$$

- ✓ first term is uniform, so let

$$C_\Delta(x, y, t) = e^{-\alpha t} [C_1(y) + C_2(\xi, y)], \quad \xi = x^{3/2},$$

where C_1 is our uniform solution above.

- embed into semi-infinite range, use mass action law for B_1

$$\frac{\partial^2 C_2}{\partial y^2} = 3F\xi y \frac{\partial C_2}{\partial \xi} - Fy^2 \frac{\partial C_2}{\partial y}, \quad C_2(\xi, \infty) = 0,$$

$$C_2(\xi, 0) = -\frac{e^{\alpha t}}{1 - B_0} \left(\frac{\partial B_1}{\partial t} + \alpha B_1 \right) - C_1(0) \equiv g(\xi),$$

$$\frac{\partial C_2}{\partial y}(\xi, 0) = \alpha B_i(\xi) H(1 - \xi)$$

- g is key to solution for B_1

$$B_1(x, t) = -e^{-\alpha t} \left\{ \frac{1 - e^{-\alpha t}}{\alpha} \left[\frac{1}{\alpha} - B_i(x) \right] + \frac{tK}{\alpha} \right\} \left[\frac{\Gamma(1/3)}{3^{2/3} F^{1/3}} + g \right]$$

- ✗ expression is secular

- ✓ most experiments run for $t = o(\text{Da}^{-1})$

Solving for the Analyte

- introduce of a Mellin transform in the ξ -direction:

$$\mathcal{M}(a) = \hat{a}(\lambda) = \int_0^{\infty} \xi^{\lambda-1} a(\xi) d\xi,$$

$$\mathcal{M}^{-1}(\hat{a}) = a(\xi) = \frac{1}{2\pi i} \int_c \hat{a}(\lambda) \xi^{-\lambda} d\lambda$$

$$\frac{d^2 \hat{C}_2}{dy^2} = -3F\lambda y \hat{C}_2 - Fy^2 \frac{d\hat{C}_2}{dy}, \quad \hat{C}_2(0) = \hat{g}, \quad \hat{C}_2(\infty) = 0$$

$$\hat{C}_2 = ye^{-\eta} \frac{\hat{g} F^{1/3} \Gamma(1-\lambda)}{3^{1/3} \Gamma(1/3)} U\left(1-\lambda, 4/3, \frac{Fy^3}{3}\right)$$

- U is a Kummer function
- must solve for g to obtain B_1

$$\hat{g} = - \left[\frac{\Gamma(1/3)}{3^{2/3} F^{1/3} \Gamma(2/3)} \right] \frac{\Gamma(2/3 - \lambda)}{\Gamma(1 - \lambda)} \frac{\partial \hat{C}_2}{\partial y}(0),$$

$$g(x) = - \frac{3^{1/3} \alpha}{2F^{1/3} \Gamma(2/3)} \int_0^x \frac{B_1(x')}{(x^{3/2} - x'^{3/2})^{2/3}} dx'$$

Particular Nonuniformities

Let $B_i(x)$ be even and analytic:

$$B_i(x) = \sum_{n=0}^{\infty} b_n x^{2n}.$$

Then

$$g(x) = - \sum_{n=0}^{\infty} b_n \frac{\Gamma((4n+2)/3) \Gamma(1/3)}{3^{2/3} F^{1/3} \Gamma(1+4n/3) \Gamma(2/3)} (\alpha x^{2n}).$$

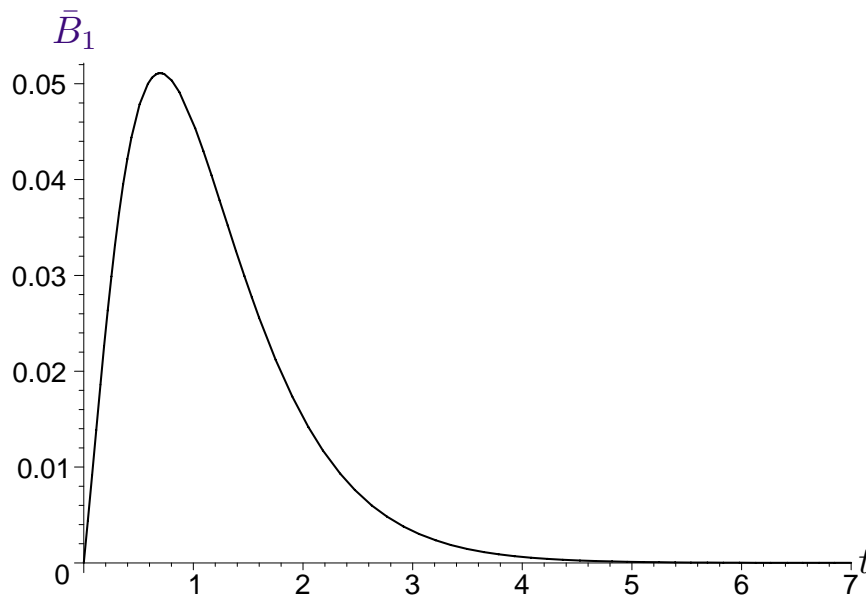
Specific Results

$$B_i(x) = 1 - x^2$$

$$\bar{B}_0(t) = \frac{1 + Ke^{-\alpha t}}{\alpha} - \frac{7}{27}e^{-\alpha t}$$

$$\bar{B}_1(t) = \frac{e^{-\alpha t}}{3^{2/3}F^{1/3}} \left[a_1 a_3 + \frac{7}{27}(a_2 a_3 + a_1 a_4) + \frac{61 a_2 a_4}{405} \right]$$

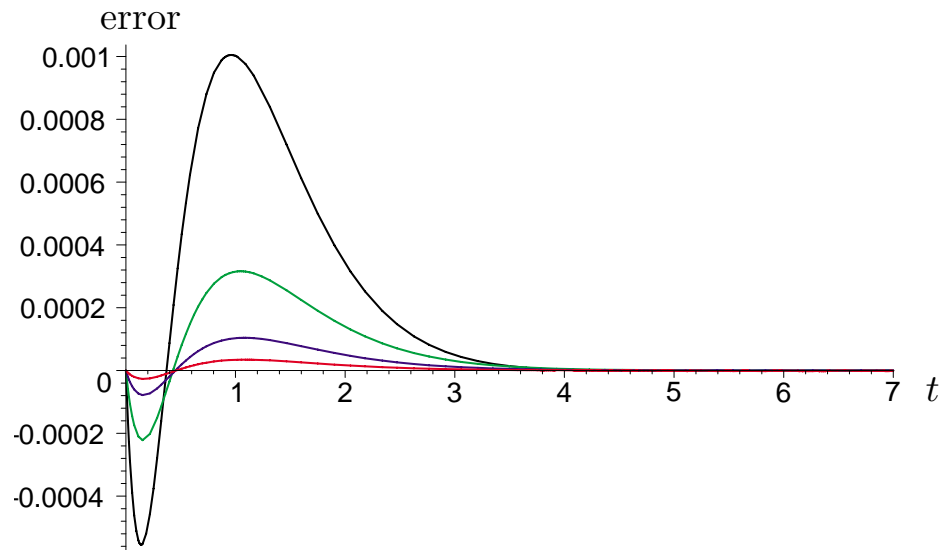
$$a_1 = \frac{K}{\alpha}(t - a_2), \quad a_2 = \frac{1 - e^{-\alpha t}}{\alpha}, \quad a_3 = K\Gamma(1/3), \quad a_4 = -\frac{9\alpha}{4\Gamma(2/3)}$$



\bar{B}_1 vs. t for $K = 1$

- ✓ significant departure from leading-order case
- ✗ This is a significant complication. Given that we are going to take an average of B_1 anyway, how close will we get if we take the average of B_i and then use the simple nonuniform case?

Averaging the Initial Data



error between averaged first and averaged last *vs.* t for $K = 1$,
 $\text{Da} = 0.005, 0.015, 0.045$, and 0.135 .

- ✓ excellent agreement obtained with much less work

Moderate Da

- ✗ can no longer use perturbation series

$$g(x, t) = \frac{1}{\text{Da}} \left[1 - \frac{1}{1-B} \left(\frac{\partial B}{\partial t} + KB \right) \right]$$

$$g = \frac{3^{1/3}}{2F^{1/3}\Gamma(2/3)} \int_0^x \frac{1}{(x^{3/2} - x'^{3/2})^{2/3}} \frac{\partial B}{\partial t}(x', t) dx'$$

$$1 - \frac{\partial B}{\partial t} - \alpha B = \frac{3^{1/3}\text{Da}(1-B)}{2F^{1/3}\Gamma(2/3)} \int_0^x \frac{1}{(x^{3/2} - x'^{3/2})^{2/3}} \frac{\partial B}{\partial t}(x', t) dx'$$

- ✗ cannot solve analytically
- ✓ future work: solve numerically, as in [4]

Conclusions

- To measure rate constants, one must have a way to collect data without disturbing the reaction and a mathematical model to interpret the data.
- ✓ The IAsys takes data without disturbing the reaction.
- ✗ However, transport effects can affect the model, especially in the limit of fast reactions (moderate Da).
- System simplified to reaction about a stagnation point.
- ✓ If initial condition is uniform (normal case), exact effective rate constant equation is obtained.
- ✗ Simple result is specific to stagnation point flow.
- ✓ If initial condition is nonuniform, asymptotic results may be obtained in the small Da limit (most common case experimentally).
- Moderate Da case (rarer experimentally) may be analyzed numerically.
- Want more details? See [2].

Further Research

- Solve moderate Da case numerically.
- More realistic model for flow field.
- Utilize nonuniform initial data techniques to analyze more complicated flows.
- Optimize device parameters.
- Examine depletion effects.
- In other devices, receptors are embedded in a thin convection-free layer [2]. How accurate is it to approximate this layer by a boundary condition?

References

- [1] Edwards, D. A. “Estimating Rate Constants in a Convection-Diffusion System with a Boundary Reaction.” *IMA Journal on Applied Mathematics*, **63** (1999): 89–112.
- [2] Edwards, D. A. “Surface Reaction Near a Stagnation Point.” Accepted to *Studies in Applied Mathematics*.
- [3] Edwards, D. A., Goldstein, B., and Cohen, D. S. “Transport Effects on Surface-Volume Biological Reactions.” *Journal of Mathematical Biology*, **39** (1999): 533–61.
- [4] Edwards, D. A., and Jackson, S. A. “Testing the Validity of the Effective Rate Constant Approximation for Surface Reaction with Transport.” Submitted to *Applied Mathematics Letters*.

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