Web Example 15–1 Applications of Diffusion and Reaction to Tissue Engineering

The equations describing diffusion and reaction in porous catalysts also can be used to derive rates of tissue growth. One important area of tissue growth is in cartilage tissue in joints such as the knee. Over 200,000 patients per year receive knee joint replacements. Alternative strategies include the growth of cartilage to repair the damaged knee.

One approach currently being researched by Professor Kristi Anseth at the University of Colorado is to deliver cartilage-forming cells in a hydrogel to the damaged area, such as the one shown in Figure WE15-1.1.

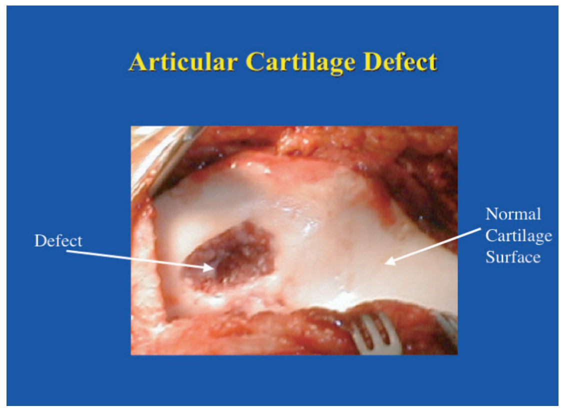

Figure WE15-1.1 Damaged cartilage. (Photo of "Damaged cartilage" originally appeared in "21 Million Americans Suffer from Arthritis," by Jerry Adler. *Newsweek*, September 3, 2001.)

Here, the patient's own cells are obtained from a biopsy and embedded in a hydrogel, which is a cross-linked polymer network that is swollen in water. In order for the cells to survive and grow new tissue, many properties of the gel must be tuned to allow diffusion of important species in and out (e.g., nutrients *in* and cell-secreted extracellular molecules such as collagen *out*). Because there is no blood flow through the cartilage, oxygen transport to the cartilage cells is primarily by diffusion. Consequently, the design must be such that the gel can maintain the necessary rates of diffusion of nutrients (e.g., O_2) into the hydrogel. These rates of exchange in the gel depend on the geometry and the thickness of the gel. To illustrate the application of chemical reaction engineering principles to tissue engineering, we will examine the diffusion and consumption of one of the nutrients, oxygen.

Our examination of diffusion and reaction in catalyst pellets showed that in many cases the reactant concentration near the center of the particle was virtually zero. If this condition were to occur in a hydrogel, the cells at the center would die. Consequently, the gel thickness needs to be designed to allow rapid transport of oxygen.

Let's consider the simple gel geometry shown in Figure WE15-1.2.

We want to find the gel thickness at which the minimum oxygen consumption rate is 10^{-13} mol/cell/h. The cell density in the gel is 10^{10} cells/dm^3, the bulk concentration of oxygen ($z = 0$) is 2×10^{-4} mol/dm^3, and the diffusivity is 10^{-5} cm^2/s.

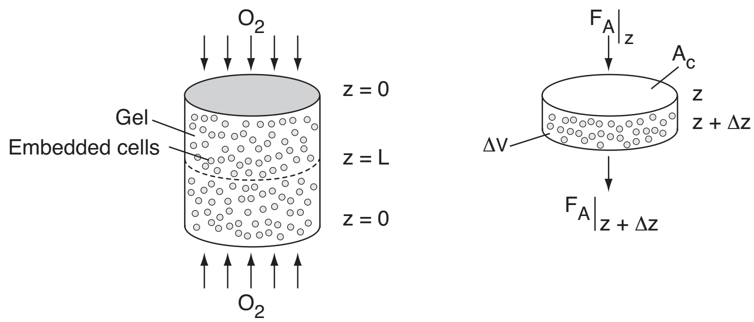

Figure WE15-1.2 Schematic of cartilage cell system.

Solution

A mole balance on oxygen, A, in the volume $\Delta V = A_c \Delta z$ is

$$F_A|_z - F_A|_{z+\Delta z} + r_A A_c \Delta z = 0 \quad \text{(WE15-1.1)}$$

Dividing by $A_c\Delta z$ and taking the limit as $\Delta z \to 0$ gives

$$\frac{1}{A_c}\frac{dF_A}{dz} + r_A = 0 \quad \text{(WE15-1.2)}$$

using Equation (14-14) for F_{Az}

$$F_A = A_c W_{Az} = A_c\left[-D_{AB}\frac{dC_A}{dz} + UC_A\right] \quad \text{(WE15-1.3)}$$

For dilute concentrations we neglect UC_A and combine Equations (WE15-1.2) and (WE15-1.3) to obtain

$$\boxed{D_{AB}\frac{d^2C_A}{dz^2} + r_A = 0} \quad \text{(WE15-1.4)}$$

If we assume the O_2 consumption rate is zero order, then

$$D_{AB}\frac{d^2C_A}{dz^2} - k = 0 \quad \text{(WE15-1.5)}$$

To learn which groups of parameters or dimensionless numbers are important in this system, we put our equation in dimensionless form by letting $\psi = C_A/C_{A0}$ and $\lambda = z/L$, and we obtain

$$\frac{d^2\psi}{d\lambda^2} - \frac{kL^2}{D_{AB}C_{A0}} = 0 \quad \text{(WE15-1.6)}$$

Recognizing the second term is just the ratio of a reaction rate to a diffusion rate for a zero-order reaction, we call this ratio the Thiele modulus, ϕ_0.

$$\phi_0 = \frac{kA_cL}{A_C D_{AB}\frac{(C_{A0}-0)}{L}} = \frac{\text{“A” Reaction rate}}{\text{“A” Diffusion rate}}$$

We divide and multiply by two to facilitate the integration

$$\boxed{\phi_0 = \frac{k}{2D_{AB}C_{A0}}L^2} \tag{WE15-1.7}$$

$$\boxed{\frac{d^2\psi}{d\lambda^2} - 2\phi_0 = 0} \tag{WE15-1.8}$$

The boundary conditions are

At $\quad \lambda = 0 \quad \psi = 1 \quad C_A = C_{A0}$ (WE15-1.9)

At $\quad \lambda = 1 \quad \frac{d\psi}{d\lambda} = 0$ Symmetry condition (WE15-1.10)

Recall that at the midplane ($z = L$, $\lambda = 1$) we have symmetry so that there is no diffusion across the midplane; thus the gradient is zero at $\lambda = 1$.

Integrating Equation (WE15-1.8) once yields

$$\frac{d\psi}{d\lambda} = 2\phi_0\lambda + K_1 \tag{WE15-1.11}$$

Using the symmetry condition, i.e., Equation (WE15-1.10), that there is no gradient across the midplane, Equation (WE15-1.10), gives $K_1 = -2\phi_0$

$$\frac{d\psi}{d\lambda} = 2\phi_0(\lambda - 1) \tag{WE15-1.12}$$

Integrating a second time gives

$$\psi = \phi_0\lambda^2 - 2\phi_0\lambda + K_2$$

Using the boundary condition $\psi = 1$ at $\lambda = 0$, we find $K_2 = 1$. The dimensionless concentration profile is

$$\boxed{\psi = \phi_0\lambda(\lambda - 2) + 1} \tag{WE15-1.13}$$

Note: The dimensionless concentration profile given by Equation (WE15-1.13) is only valid for values of the Thiele modulus less than or equal to 1. This restriction can be easily seen if we set $\phi_0 = 10$ and then calculate ψ at $\lambda = 0.1$ to find $\psi = -0.9$, which is a negative concentration!!

Parameter Evaluation

Evaluating the zero-order rate constant, k, yields

$$k = \frac{10^{10}\text{cells}}{\text{dm}^3} \cdot \frac{10^{-13}\text{mole O}_2}{\text{cell} \cdot \text{h}} = 10^{-3}\text{mole}/\text{dm}^3 \cdot \text{h}$$

and then the ratio in Equation (WE15-1.7) is

$$\frac{k}{2C_{A0}D_{AB}} = \frac{10^{-3}\text{mol/dm}^3 \cdot \text{h}}{2 \times 0.2 \times 10^{-3}\text{mol/dm}^3 \cdot 10^{-5}\,\frac{\text{cm}^2}{\text{s}} \times \frac{3600\text{ s}}{\text{h}}} = 70\text{ cm}^{-2} \tag{WE15-1.14}$$

The Thiele modulus is

$$\boxed{\phi_0 = \frac{kL^3}{2C_{A0}D_{AB}} = 70\ \text{cm}^{-2}L^2} \tag{WE15-1.15}$$

(a) Consider the gel to be completely effective such that the concentration of oxygen is reduced to zero by the time it reaches the center of the gel. That is, if $\psi = 0$ at $\lambda = 1$, we solve Equation (WE15-1.13) to find that $\phi_0 = 1$

$$\phi_0 = 1 = \frac{70}{\text{cm}^2}L^2 \tag{WE15-1.16}$$

Solving for the gel half thickness L yields

$$L = 0.12\ \text{cm}$$

Let's critique this answer. We said the oxygen concentration was zero at the center, and the cells can't survive without oxygen. Consequently, we need to redesign so C_{O_2} is not zero at the center.

(b) Now consider the case where the minimum oxygen concentration for the cells to survive is 0.1 mmol/dm^3, which is one-half that at the surface (i.e., $\psi = 0.5$ at $\lambda = 1.0$). Then Equation (WE15-1.13) gives

$$\phi_0 = 0.5 = \frac{70L^2}{\text{cm}^2} \tag{WE15-1.17}$$

Solving Equation (WE15-1.17) for L gives

$$\boxed{L = 0.085\ \text{cm} = 0.85\ \text{mm} = 850\ \mu\text{m}}$$

Consequently, we see that the maximum thickness of the cartilage gel ($2L$) is on the order of 1 mm, and engineering a thicker tissue is challenging.

(c) One can consider other perturbations to the preceding analysis by considering the reaction kinetics to follow a first-order rate law, $-r_A = k_A C_A$, or Monod kinetics,

$$-r_A = \frac{\mu_{max}C_A}{K_S + C_A} \tag{WE15-1.18}$$

The author notes the similarities to this problem with his research on wax build-up in subsea pipeline gels.[1] Here, as the paraffin diffuses into the gel to form and grow wax particles, these particles cause paraffin molecules to take a longer diffusion path and, as a consequence, the diffusivity is reduced. An analogous diffusion pathway for oxygen in the hydrogel containing collagen is shown in Figure WE15-1.3

$$D_e = \frac{D_{AB}}{1 + \alpha^2 F_w^2/(1 - F_w)} \tag{WE15-1.19}$$

[1] P. Singh, R. Venkatesan, N. Nagarajan, and H. S. Fogler, *AIChE J.,* 46, 1054 (2000).

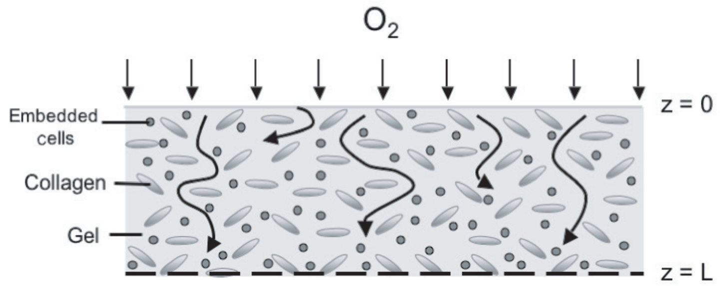

Figure WE15-1.3 Diffusion of O_2 around collagen.

where α and F_w are predetermined parameters that account for diffusion around particles. Specifically, for collagen, α is the aspect ratio of the collagen particle and F_w is weight fraction of "solid" collagen obstructing the diffusion.[1] A similar modification could be made for cartilage growth. These situations are left as an exercise in the end-of-the-chapter problems, e.g., P15-2(b).

Analysis: In this example we modeled diffusion and reaction in hydrogels to predict the oxygen concentration needed to sustain cell growth. It was found that only very thin gels will have the minimum concentration at all locations that would allow the cells to survive.

Web 15.3.3 Effectiveness Factor for Nonisothermal First-Order Catalytic Reactions

The preceding discussion of effectiveness factors is valid only for isothermal conditions. When a reaction is exothermic and nonisothermal, the effectiveness factor can be significantly greater than 1, as shown in Figure W15-7. Values of η greater than 1 occur because the external surface temperature of the pellet is less than the temperature inside the pellet where the exothermic reaction is taking place. Therefore, the rate of reaction inside the pellet is greater than the rate at the surface. Thus, because the effectiveness factor is the ratio of the actual reaction rate to the rate at surface conditions, the effectiveness factor can be greater than 1, depending on the magnitude of the parameters β and γ. The parameter γ is sometimes referred to as the Arrhenius number, and the parameter β represents the maximum temperature difference that could exist in the pellet relative to the surface temperature T_s.

$$\gamma = \text{Arrhenius number} = \frac{E}{RT_s}$$

$$\beta = \frac{\Delta T_{max}}{T_s} = \frac{T_{max} - T_s}{T_s} = \frac{-\Delta H_{Rx} D_e C_{As}}{k_t T_s}$$

Can you find regions where multiple solutions (MSS) exist?

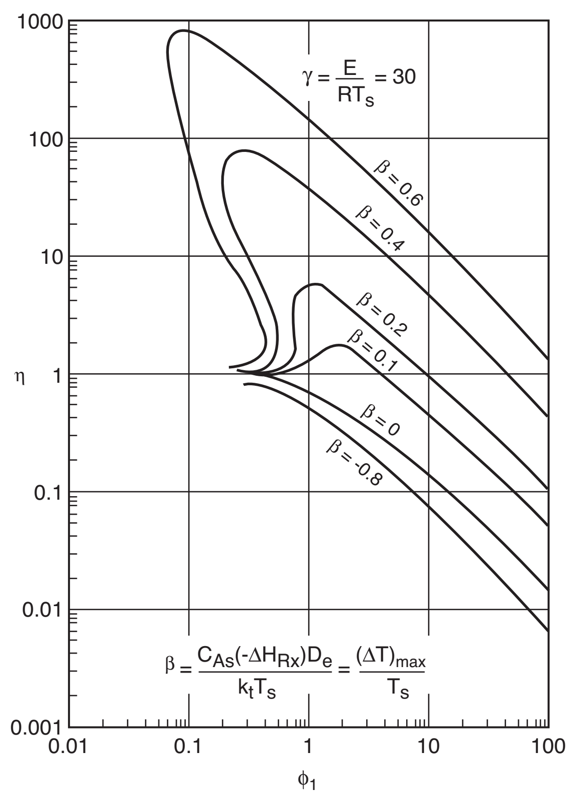

Figure W15-7 Nonisothermal effectiveness factor.

(See Web Problem P15-13_C for the derivation of β.) The Thiele modulus for a first-order reaction, ϕ_1, is evaluated at the external surface temperature. Typical values of γ for industrial processes range from a value of $\gamma = 6.5$ ($\beta = 0.025$, $\phi_1 = 0.22$) for the synthesis of vinyl chloride from HCl and acetone, to a value of $\gamma = 29.4$ ($\beta = 6 \times 10^{-5}$, $\phi_1 = 1.2$) for the synthesis of ammonia.[2] The lower the thermal conductivity k_t and the higher the heat of reaction, the greater the temperature difference (see Problems P15-13_C and P15-14_C). We observe from Figure W15-7 that multiple steady states can exist for values of the Thiele modulus less than 1 and when β is greater than approximately 0.2. There will be no multiple steady states when the criterion developed by Luss is fulfilled.[3]

Typical parameter values

Criterion for **no** MSSs in the pellet

$$\boxed{4(1+\beta) > \beta\gamma} \tag{W15-36}$$

Web Problem. Suppose we let $\gamma = 30$, $\beta = 0.4$, and $\phi_1 = 0.4$ in Figure W15-7? What would cause you to go from the upper steady state to the lower steady state and vice versa?

[2] H. V. Hlavacek, N. Kubicek, and M. Marek, *J. Catal.*, 15, 17 (1969).

[3] D. Luss, *Chem. Eng. Sci.*, 23, 1249 (1968).

Additional Homework Problems

P15-12$_C$ Reconsider diffusion and reaction in a spherical catalyst pellet for the case where the reaction is not isothermal. Show that the energy balance can be written as

$$\frac{1}{r^2}\frac{d}{dr}\left(r^2 k_t \frac{dT}{dr}\right) + (-\Delta H_R^\circ)(-r_A) = 0 \qquad \text{(P15-12.1)}$$

where k_t is the effective thermal conductivity, cal/s·cm·K of the pellet with $dT/dr = 0$ at $r = 0$, and $T = T_s$ at $r = R$.

(a) Evaluate Equation (15-11) for a first-order reaction and combine with Equation (P15-12.1) to arrive at an equation giving the maximum temperature in the pellet

$$T_{max} = T_s + \frac{(-\Delta H_{Rx}^\circ)(D_e C_{As})}{k_t} \qquad \text{(P15-12.2)}$$

Note: At T_{max}, $C_A = 0$.

(b) Choose representative values of the parameters and use a software package to solve Equations (15-11) and (P15-12.1) simultaneously for $T(r)$ and $C_A(r)$ when the reaction is carried out adiabatically. Show that the resulting solution agrees qualitatively with Figure W15-7.

P15-13$_C$ Determine the effectiveness factor for a nonisothermal spherical catalyst pellet in which a first-order isomerization is taking place.

Additional information:

$A_i = 100\ m^2/m^3$
$\Delta H_R^\circ = -800{,}000$ J/mol
$D_e = 8.0 \times 10^{-8}\ m^2/s$
$C_{As} = 0.01\ kmol/m^3$
External surface temperature of pellet, $T_s = 400$ K
$E = 120{,}000$ J/mol
Thermal conductivity of pellet = 0.004 J/m·s·K
$d_p = 0.005$ m
Specific reaction rate = 10^{-1} m/s at 400 K
Density of calf's liver = 1.1 g/dm^3

How would your answer change if the pellets were 10^{-2}, 10^{-4}, and 10^{-5} m in diameter? What are typical temperature gradients in catalyst pellets?

- **Links to Additional Homework Problems**

CDP15-A$_B$ Determine the catalyst size that gives the highest conversion in a packed-bed reactor.
CDP15-B$_B$ Determine the importance of concentration and temperature gradients in a packed-bed reactor.
CDP15-C$_B$ Determine the concentration profile and effectiveness factor for the first-order gas-phase reaction.

$$A \rightarrow 3B$$

Slurry Reactors
CDP15-D$_B$ Hydrogenation of methyl linoleate-comparing catalyst. [3rd Ed. P12-19]
CDP15-E$_B$ Hydrogenation of methyl linoleate. Find the rate-limiting step. [3rd Ed. P12-20]
CDP15-F$_B$ Hydrogenation of 2-butyne–1,4-diol to butenediol. Calculate the percent resistance of total for each step and the conversion. [3rd Ed. P12-21]
CVD Boat Reactors
CDP15-G$_D$ Determine the temperature profile to achieve a uniform thickness. [2nd Ed. P11-18]
CDP15-H$_B$ Explain how varying a number of the parameters in the *CVD boat reactor* will affect the wafer shape. [2nd Ed. P11-19]
CDP15-I$_B$ Determine the wafer shape in a CVD boat reactor for a series of operating conditions. [2nd Ed. P11-20]
CDP15-J$_C$ Model the build-up of a silicon wafer on parallel sheets. [2nd Ed. P11-21]
CDP15-K$_C$ Rework the CVD boat reactor accounting for the reaction

$$SiH_4 \rightleftarrows SiH_2 + H_2$$

[2nd ed. P11-22]
Trickle Bed Reactors
CDP15-L$_B$ Hydrogenation of an unsaturated organic is carried out in a *trickle bed reactor*. [2nd Ed. P12-7]
CDP15-M$_B$ The oxidation of ethanol is carried out in a *trickle bed reactor*. [2nd Ed. P12-9]
CDP15-N$_C$ Hydrogenation of aromatics in a *trickle bed reactor*. [2nd Ed. P12-8]
Fluidized Bed Reactors
CDP15-O$_C$ Open-ended fluidization problem that requires critical thinking to compare the two-phase fluid models with the three-phase bubbling bed model.
CDP15-P$_A$ Calculate reaction rates at the top and the bottom of the bed for Example R15.3-3.
CDP15-Q$_B$ Calculate the conversion for $A \rightarrow B$ in a bubbling fluidized bed.
CDP15-R$_B$ Calculate the effect of operating parameters on conversion for the reaction-limited and transport-limited operation.
CDP15-S$_B$ *Excellent Problem* Calculate all the parameters in Example R15-3.3 for a different reaction and different bed.
CDP15-T$_B$ Plot conversion and concentration as a function of bed height in a bubbling fluidized bed.
CDP15-U$_B$ Use RTD studies to compare a bubbling bed with a fluidized bed.
CDP15-V$_B$ New problems on the CRE Web site.
CDP15-W$_B$ Green Engineering, *www.rowan.edu/greenengineering*.

Green Engineering