On parameter estimation in a diffusion process with piecewise constant coefficients

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Abstract: In this report we describe a diffusion equation with piecewise constant coefficients modelling the penetration process of drugs through thin membranes. Its solution can, in some special cases, be written as a Fourier series. In general, however, numerical techniques are required. We derive a finite volume discretization and apply it to data from FTIR-ATR spectroscopy to obtain estimates for the effective diffusion rates.

Keywords: linear diffusion equation, finite volumes, attenuated total reflectance spectroscopy

1 Introduction

Fig. 1 depicts a diffusion cell. It is used in pharmaceutical research to estimate the rate by which certain drugs travel through thin membranes which shall resemble the outmost layer of the skin (*stratum corneum*). For simplicity, we assume that the diffusion is homogeneous within the two compartments and that the concentration of the agent in the donator is constant over time.

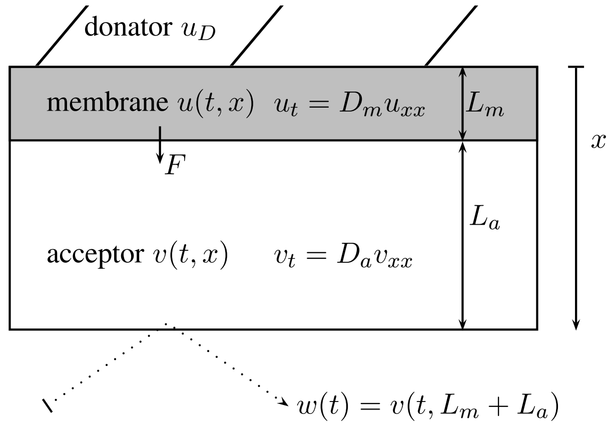

Fig 1.: Schematic representation of the diffusion cell

A quantity $w(t)$ proportional to the concentration of the diffusant at the bottom of the acceptor can be measured using Fourier transformed infrared attenuated total reflection (FTIR-ATR). If the transport process

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is an idealised diffusion, $w(t)$ will exponentially approach a stationary value proportional to the donator concentration u_D,

$$w(t) \approx u_D(1 - c_1 \exp(-\alpha t)), \quad t \gg 0, \tag{1}$$

with a constant $c_1 \approx 1$ describing the proportion of the slowest eigenmode in the initial condition.
We assume that the measured data fits to this model (1) well enough to estimate α reliably. This means, in particular, that we record $w(t)$ over a relatively long period that its final value is almost at steady state. The parameter α represents the time scale of the process and will depend on the two diffusion constants D_m and D_a of membrane and acceptor. It is the purpose of this paper to explore the precise relation between α and D_m while all the other parameters D_a, L_m and L_a are fixed and known.
The paper is organized as follows. The transport of the substance through the cell is mathematically described by a linear, one-dimensional diffusion equation with a piecewise constant diffusion constant in Section 2. We will also discuss analytic solutions in certain special cases. In Section 3, a finite volume semidiscretization of the partial differential equation is derived and used to predict $w(t)$. In Section 4, diffusion rates for two sets of experimental data (for urea and taurine) are computed.

2 A mathematical model for the cell

A mathematical model for the cell is obtained by coupling two diffusion equations: one for the concentration $u(t,x)$ of the diffusant in the membrane and one for the concentration $v(t,x)$ in the acceptor. Denote F the flux leaving the membrane. Then, by Fick's diffusion law, $F = D_m u_x(t, L_m) = D_a v_x(t, L_m)$. Together, this gives the system

$$u_t = D_m u_{xx}, \quad x \in (0, L_m), \tag{2a}$$

$$v_t = D_a v_{xx}, \quad x \in (L_m, L_a), \tag{2b}$$

$$u(t, 0) = u_D, \quad v_x(t, L_m + L_a) = 0, \tag{2c}$$

$$0 = D_m u_x(t, L_m) - D_a v_x(t, L_m), \tag{2d}$$

$$0 = u(t, L_m) - v(t, L_m), \tag{2e}$$

$$u(0, x) = 0, \quad x \in (0, L_m), \quad v(0, x) = 0. \tag{2f}$$

Eq. (2c) describes the boundary conditions, Eq. (2d,2e) the coupling and Eq. (2f) the initial condition. It is often more convenient to work homogeneous boundary conditions because solutions can then be composed additively. In our case, this corresponds to defining quantities

$$\widehat{u}(t, x) = (u_D - u(t, x))/u_D, \tag{3a}$$

$$\widehat{v}(t, x) = (u_D - v(t, x))/u_D, \tag{3b}$$

$$\widehat{w}(t) = (u_D - w(t))/u_D. \tag{3c}$$

Before we describe numerical techniques for the general solution in the next section, we recall briefly some analytic results for system (2) in two special cases. The first is, that we only have an acceptor but no diffusion barrier due to a membrane; and the second, that the diffusion in the acceptor is much faster than the diffusion in the membrane. For convenience, we will use the transformed quantities $\widehat{u}(t, x)$ instead of $u(t, x)$.

First case. If the membrane is very porous (as it will be if it not coated) it provides, essentially, no barrier for the diffusant. Thus we can use this case to estimate the diffusion in the acceptor. Eq. (2) reduces to the classical diffusion equation

$$\widehat{v}_t = D_a \widehat{v}_{xx},$$
$$\widehat{v}(0,t) = 0, \quad \widehat{v}_x(0, L_a) = 0, \quad \widehat{v}(0,x) = 1,$$

with the well-known solution

$$\widehat{v}(x,t) = \sum_{\substack{k=1 \\ k \text{ odd}}}^{\infty} \frac{4}{\pi k} \exp\left(-\frac{k^2\pi^2}{4}\frac{D_a}{L_a^2}t\right) \sin\left(\frac{k}{2L_a}\pi x\right),$$

and from using the first term with $k = 1$ only, we find the approximation formula

$$w(t) = u_D \left(1 - \frac{4}{\pi} \exp\left(-\frac{\pi^2}{4}\frac{D_a}{L_a^2}t\right)\right). \tag{4}$$

Comparing Eq. (4) with Eq. (1) gives the formula

$$D_a = 4\alpha L_a^2/\pi^2 \tag{5}$$

for the diffusion constant for the acceptor.

Second case. The diffusion in the acceptor is, in our application, often much faster than the diffusion in the membrane. We have therefore studied the special case of system (2) where $D_a \to \infty$. This reduces the partial differential equation for $v(t,x)$ to an ordinary differential equation for the acceptor concentration $v(t)$ coupled with $u(t,x)$ at $x = L_m$ with a dynamic boundary condition, $v'(t) = -\frac{D_m L_m}{L_a} u_x(t, L_m)$, $v(0) = 0$. Nevertheless, a Fourier series

$$\widehat{u}(t,x) = \sum_{k=1}^{\infty} c_k \exp\left(-\lambda_k^2 \frac{D_m}{L_m^2}t\right) \sin(\lambda_k \frac{x}{L_m}) \tag{6}$$

for the solution can be found here, too. For details see [1,2]. The eigenvalues λ_k in (6) are defined implicitly by

$$\frac{\lambda_k L_a}{L_m} \sin(\lambda_k) - \cos(\lambda_k) = 0, \quad \frac{\lambda_k}{\pi} \in [(k-1), (k - \frac{1}{2})],$$

and $c_k = 2/\left(\lambda_k(1 + (L_a/L_m)\sin^2(\lambda_k))\right)$. For $t \gg 0$ it is again sufficient to consider only the effect of the first eigenvalue/eigenvector pair. This leads to a relation between α and D_m for the form

$$D_m = \alpha L_m^2/\lambda_1^2, \tag{7}$$

which is still linear. A further simplification can be made if the diffusion in the acceptor is fast *and* the membrane is thin, i.e. when L_m is small compared to L_a. The concentration $u(t,x)$ will then decline linearly with x leading to the single ordinary differential equation $w'(t) = -(D_m/(L_a L_m))(w(t) - u_D)$ with $w(0) = 0$ and, hence, to the approximation formula

$$D_m \approx \alpha L_m L_a. \tag{8}$$

3 Numerical solution

To find a numerical solution for the system (2), we first discretize $\widehat{u}(t,x)$ and $\widehat{v}(t,x)$ in space using finite volumes, see Fig. 2 (and, e.g., [3] for a general description of this technique). Membrane and acceptor are partitioned into cells with average concentrations $u^i(t)$ and $v^i(i)$. The cells are centered at $h_m i$, $i = 0,\dots,n_m$ and at $L_m + (1/2+i)h_m$, $i = 1,\dots,n_a$ with $h_m = L_m/(n_m+1/2)$ and $h_a = L_a/n_a$.

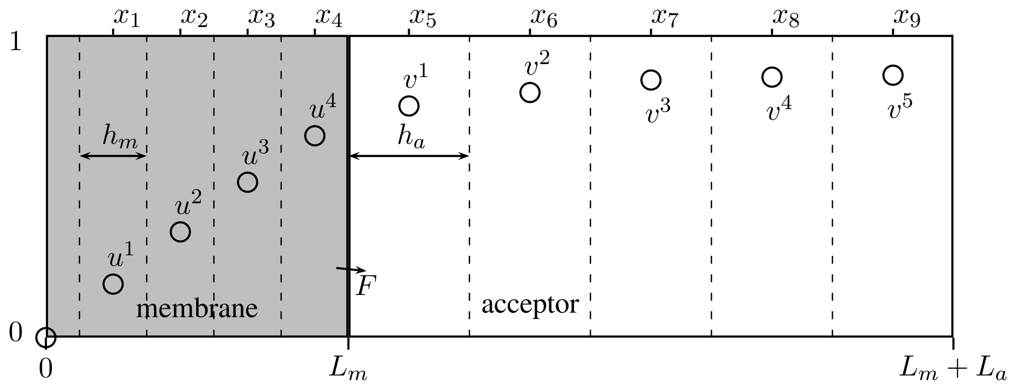

Fig 2.: Semidiscretization of $\widehat{u}(t,x)$ and $\widehat{v}(t,x)$ with finite volumes ($n_m = 4$, $n_a = 5$)

We collect $u^i(t)$ and $v^i(t)$ in a vector of length $n_m + n_a$,

$$U(t) = [u^1(t),\, u^2(t),\, \dots,\, u^{n_m}(t),\, v^1(t),\, v^2(t),\, \dots,\, v^{n_a}(t)].$$

Note, that $U(t)$ contains both: concentrations in the membrane and in the acceptor. Its last component $\widehat{w}(t) \approx e^T_{n_m+n_a} U(t)$ is the quantity corresponding to the measured data. Using standard difference formulae to approximate in- and outgoing fluxes leads to an ordinary differential equation

$$\frac{d}{dt}U(t) = MU(t), \quad \text{with} \tag{9}$$

$$U(0) = [1,1,\dots,1]^T =: \mathbb{1}^T, \tag{10}$$

where

$$M = \operatorname{diag}\left(D_m/h_m^2 M_1, D_a/h_a^2 M_2\right) + R \tag{11}$$

with

$$M_1 = \begin{bmatrix} -2 & 1 & & & \\ 1 & -2 & 1 & & \\ & \ddots & \ddots & \ddots & \\ & & 1 & -2 & 1 \\ & & & 1 & -1 \end{bmatrix}, \quad M_2 = \begin{bmatrix} -1 & 1 & & & \\ 1 & -2 & 1 & & \\ & \ddots & \ddots & \ddots & \\ & & 1 & -2 & 1 \\ & & & 1 & -1 \end{bmatrix}.$$

Matrix R corresponds to the flux between membrane and acceptor. If F it is approximated by

$$F = r(v^1(t) - u^{n_m}(t)), \quad r = 2\frac{D_m D_a}{h_a D_m + h_m D_a},$$

then, R has only four non-zero elements

$$R_{n_m:n_m+1,n_m:n_m+1} = \begin{bmatrix} -r/h_m & r/h_m \\ r/h_a & -r/h_a \end{bmatrix}.$$

Note, that this choice reduces to the standard stencil if $D_m = D_a$ and $h_m = h_a$. The solution for Eq. (9) is

$$U(t) = \exp(Mt)\mathbb{1} = T\exp(\Lambda t)T^{-1}\mathbb{1} \tag{12}$$

with a diagonalization $T^{-1}MT = \Lambda = \mathrm{diag}(\lambda_1, \ldots, \lambda_{n_m+n_a})$ with $|\lambda_1| < |\lambda_2| < \cdots < |\lambda_{n_m+n_a}|$. The asymptotic behaviour of the solution is determined by the first eigenvalue λ_1 and the corresponding eigenvector Te_1, i.e. $U(t) \approx Te_1 \exp(\lambda_1 t)T^{-1}\mathbb{1}$ for $t \gg 0$. Comparing the last component of $U(t)$ with with Eq. (1) gives $\alpha = -\lambda_1$ and $c_1 = T_{n_m+n_a,1}T^{-1}\mathbb{1}$

Remark 1. Because R has rank 1, a divide-and-conquer algorithm (as described in [4], pp. 459) can be used to compute the eigenvalues of M even this matrix fails to be symmetric. For this, we can take advantage of the analytic knowledge about the eigenvalues and eigenvector of the two matrices M_1 and M_2. Unfortunately, the final synthesis step cannot be computed analytically and we therefore do not obtain a nice analytic formula for λ_1.

4 Examples and results

Material and methods

We used circular polycarbonate membranes (Avestin Lipofast, Ottawa, Canada) with $1000\,\mathrm{nm}$ pores. Untreated, these membranes are almost perfectly penetrable by the two considered diffusants, urea and taurine. Coating with a compound of ceramide [AP] 55, cholesterol 25, palmitinic acid 15 and cholesterol sulfate sodium salt 5 (% w/w) increases their thickness and reduced the transmissibility. To compute an effective diffusion constant for the coated membrane we ignored its inner structure and treated it, for simplicity, as it was homogeneous. The height of the acceptor was $L_a = 1640\mu\mathrm{m}$ (a volume of $V = 90\,\mu\mathrm{l}$ in a cylinder with diameter $d = 7000\,\mu\mathrm{m}$).
The program code for the data fitting, for generating matrix M in (9) and for finding the optimal D_m was written in Matlab and can be requested from the authors.

Results

A typical (normalized) data set is shown in Fig. 3. The deviation of the measured values from the exponential model $w(t) = u_D(1 - c_1\exp(-\alpha t))$ is only slight.

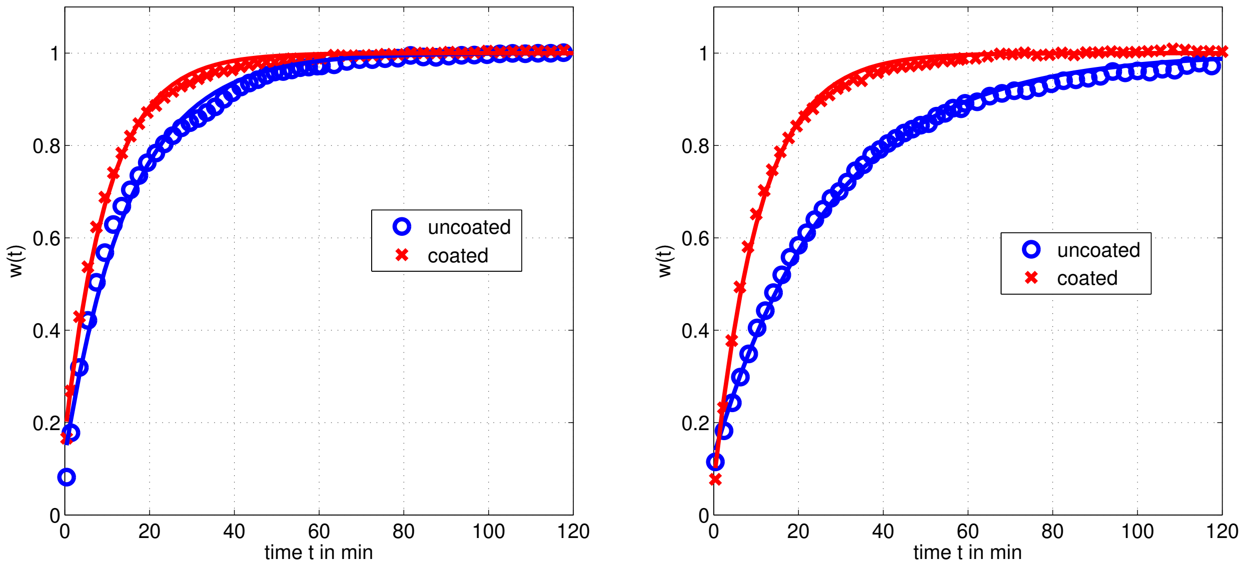

Fig. 3.: Observed FIR-ATR data together with fitted curves according to the exponential model $w(t) = 1 - c_1 \exp(-\alpha t)$. Left: urea, Right: taurine.

The fitted values for α, which are shown in Tab. 1 are obtained by using standard nonlinear least-squares techniques. It is a three parameter fit because c_1 and u_D are also unknown and computed simultaneously. Since parameter c_1 describes the initial condition at the beginning of the experiments and it is *not* related to the diffusion rate and therefore not needed to compute D_m.

Tab. 1.: Fitting results for experiments with urea and taurine (units: μm, min^{-1} and $\mu\text{m}^2\text{min}^{-1}$)

	Urea		**Taurine**	
	coated	uncoated	coated	uncoated
L_m	21	11	17	12
L_a	1400	1400	1400	1400
α	0.0656	0.0982	0.0356	0.0920
D_m	6000		1500	
D_a	107000	107000	100000	10000

Using the uncoated membrane, we first compute the diffusion constant in the acceptor by formula (5) and then D_m using the semidiscretized model of Section 3, see Tab. 1.

Now it is possible to answer the question about the relation between α and D_m, see Fig. 4 (left). We change α arbitrarily and compute the smallest eigenvalue of the corresponding matrix M. It is clearly seen that the approximation formula (8) (dashed line) is accurate for small α. It is also seen that the inverse problem of finding a D_m for a given α is well conditioned if α is not too big. However, if the diffusion rate in the membrane is very big it has no effect on α. It is intuitively clear why: all we measure is the diffusion in the acceptor.

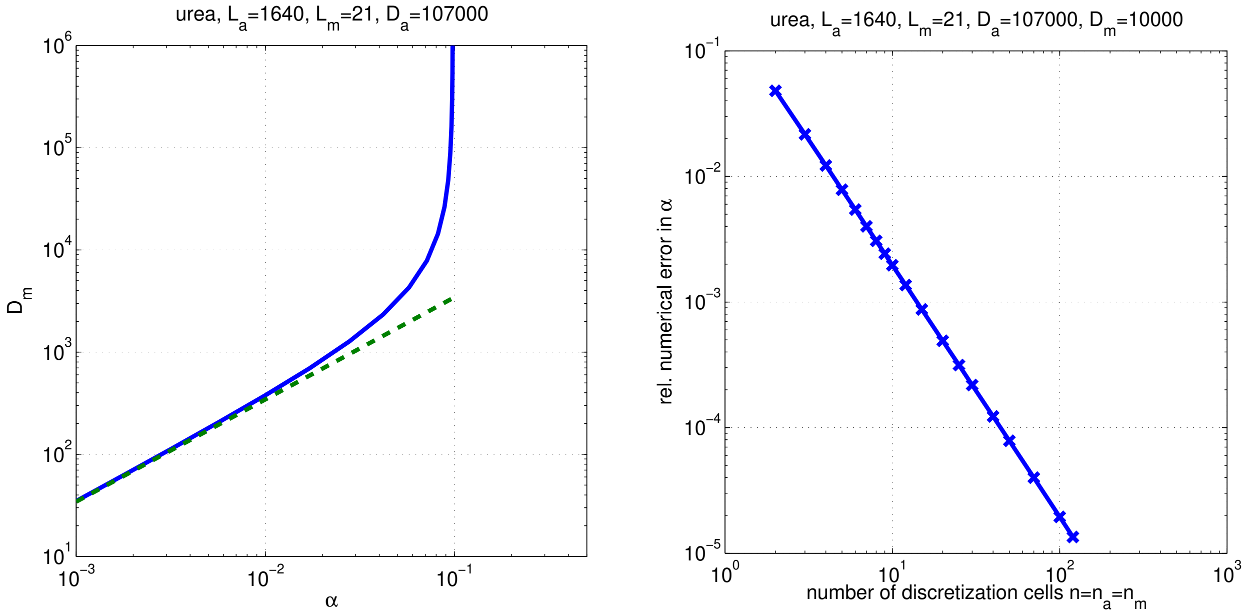

Fig 4.: Left: Relation between α and D_m. The straight line corresponds to the approximation formula (8). Right: Second order convergence of $\alpha = -\lambda_1(M)$, $n = n_m = n_a$ denotes the number of finite volume cells in the membrane and in the acceptor.

Finally, we want to check the accuracy of our computations. Since all eigenvalues are computed to machine precision, the numerical error is completely determined by the resolution of the grid. In Fig. 4 (right), we see that the spatial discretization has order 2. With $n_m = n_a = 10$ the relative error is about 10^{-3} and certainly small enough for our application.

5 Conclusions

By coupling diffusion equations for membrane and acceptor, we have derived a mathematical model for our diffusion cell. Using finite volume discretization and an eigenvalue analysis for the semidiscrete system we have estimated effective diffusion constant for the FTIR-ATR cell. The computation consists of two steps: (a) a nonlinear least squares fit of the data with an exponential model and (b) the generation of a matrix M that it smallest eigenvalue matches the parameter from the fit.

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References

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A Matlab and Mathematica codes

Our first Matlab program is for solving the direct problem that is to compute α from given diffusion rates D_a and D_m. Although c_1 is strictly speaking not needed in our application, we compute it as well. To do this accurately, we have to compute an eigensystem for M, or, at least, a subsystem for the first few dominant eigenvalues.

```
% COMPUTEALPHA  Compute slowest eigenmode for an equation with
%                picewise constant diffusion coefficients.
%
%  [alpha,c1]=compute_alpha(La,Lm,Da,Dm) assembles the matrix M for
%  the ODE y'=M y  and computes it smallest eigenvalue alpha. Lm
%  and Dm are the thickness and the diffusion coefficient of the
%  membrane, La and Da represent the acceptor. The model for the
%  FIR-ATR data is w(t)=u_D(1-c1*exp(-alpha t)).
%  -------------------------------------------------------------

function [alpha,c1]=computealpha(La,Lm,Da,Dm)

nm=10; na=10; % spacial grid

ldm=nm+na; hm=Lm/(nm+1/2); ha=La/na;
T=repmat([1,-2,1],ldm,1);
T(end-1,1)=1;T(end,2)=-1;

T([nm,nm+1],:)=[0,-1,1;
                1,-1,0];
M=spdiags(T,-1:1,ldm,ldm);
M(1:nm,:)=Dm/hm^2*M(1:nm,:);
M(nm+1:end,:)=Da/ha^2*M(nm+1:end,:);

r=2*Dm*Da/(ha*Dm+hm*Da);
b=nm+[0,1]; M(b,b)=M(b,b)+[[-r,r]/hm;[r,-r]/ha];

[V,D]=eigs(M,min(ldm-2,20),'sm',struct('disp',0));
c=(V\ones(ldm,1))*V(end,1);c1=c(1);
alpha=-D(1,1);
```

The inverse problem of finding the corresponding D_m for a given value of α (determined by the measured data) can be written as a root finding problem for which the built-in `fminsearch` quickly finds the solution for the problem is monotone (cf. Fig. 4, left).

```
% COMPUTEDM Computes the diffusion rate in the membrane
%           that it fits to a given value of alpha.
%
% Dm=computedm(La,Lm,Da,alpha) computes the
% root x of f(x)=computealpha(La,Lm,Da,x)-alpha.
%
% The inital guess for x is alpha*Lm*La.
% -----------------------------------------------

function Dm=computedm(La,Lm,Da,alpha)
Dm=fminsearch(@(x)abs(computealpha(La,Lm,Da,x)-alpha),alpha*Lm*La);
```

The implementation of the direct problem in Mathematica is straightforward, however less elegant and less efficient than in Matlab.

```
<< LinearAlgebra`MatrixManipulation`

alpha[La_, Lm_, Da_, Dm_] := Module[
  {nm = 10, na = 10, n, hm, ha, r, g, f, M, L, V},
  n = nm + na;
  hm = Lm/(1/2 + nm); ha = La/na;
  r = 2 Da Dm/(ha Dm + hm Da);

  g[i_] := If[i <= nm, Dm/hm^2, Da/ha^2];

  f[n, n - 1] := 1 g[n];
  f[n, n ]  := - 1 g[n];
  f[i_, i_] := -2 g[i];
  f[i_, j_] := 1 g[i];

  f[nm, nm] := -1 g[nm] - r/hm;
  f[nm, nm + 1] := r/hm;
  f[nm + 1, nm] := r/ha;
  f[nm + 1, nm + 1] := -1 g[nm + 1] - r/ha;

  M = TridiagonalMatrix[f, n];
  {L, V} = Eigensystem[N[M]];
  {alpha -> -Last[L],
   c1 -> Last[(Inverse[Transpose[V]].Table[1, {n}])V[[n, n]]]}
]
```