Some Linear Algebra Problems from Mathematical Biology

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Ordinary Differential Equations

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$P(\lambda) = Det(\lambda I - J) = \lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + \cdots + a_{n-1}\lambda + a_n$
Stable: if all eigenvalues have negative real parts

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$n = 3$: $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$, $\underline{a_1 > 0,\ a_2 > \frac{a_3}{a_1},\ a_3 > 0}$

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$n = 4$: $\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0$, $\underline{a_1 > 0,\ a_2 > \dfrac{a_3^2 + a_1^2 a_4}{a_1 a_3},\ a_3 > 0,\ a_4 > 0}$

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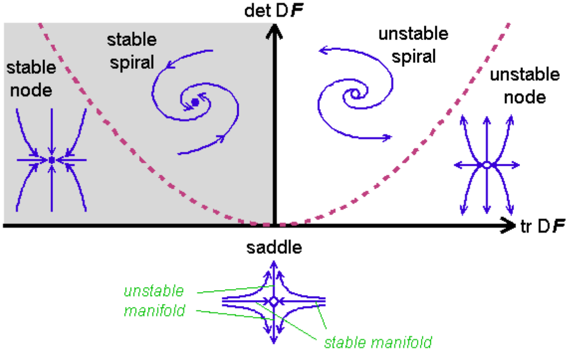
$n \geq 5$: check books
http://www.cems.uvm.edu/~lakobati/08_fall/EE_295/Routh_Hurwitz_Criterion.pdf

Trace-determinant plane



Jacobian matrix $J = \begin{pmatrix} a & b \\ c & d \end{pmatrix}$

characteristic equation
$\lambda^2 + a_1\lambda + a_2 = \lambda^2 - (a+d)\lambda + (ad - bc) = (\lambda - \lambda_1)(\lambda - \lambda_2) = 0$
$a_1 = -(a+d) = -Trace(J)$ and $a_2 = ad - bc = Det(J)$
Stability: $a_1 > 0$ and $a_2 > 0$, or $Trace(J) < 0$ and $Det(J) > 0$.

Systems

Suppose that Ω is a bounded smooth domain in $\mathbb{R}^n$ with $n \geq 1$.

$$\begin{cases} u_t = d_1 \Delta u + f(u,v), & x \in \Omega, \quad t > 0, \\ v_t = d_2 \Delta v + g(u,v), & x \in \Omega, \quad t > 0, \\ \nabla u \cdot n = \nabla v \cdot n = 0, & x \in \partial\Omega, \quad t > 0, \\ u(x,0) = u_0(x) \geq 0, \ v(x,0) = v_0(x) \geq 0, & x \in \Omega. \end{cases}$$

Suppose that $(u_*(x), v_*(x))$ is a steady state solution. Then from the Principle of Linearized Stability, we shall consider the eigenvalues of

$$\begin{cases} d_1 \Delta \phi + f_u(u_*, v_*)\phi + f_v(u_*, v_*)\psi = \mu\phi, & x \in \Omega, \\ d_2 \Delta \psi + g_u(u_*, v_*)\phi + g_v(u_*, v_*)\psi = \mu\psi, & x \in \Omega, \\ \nabla \phi \cdot n = \nabla \psi \cdot n = 0, & x \in \partial\Omega. \end{cases}$$

$(u_*(x), v_*(x))$ is locally asymptotically stable if all eigenvalues have negative real part.

Cooperative: $f_v(u,v) \geq 0$, $g_u(u,v) \geq 0$ for $(u,v) \in \mathbb{R}^+ \times \mathbb{R}^+$
Competitive: $f_v(u,v) \leq 0$, $g_u(u,v) \leq 0$ for $(u,v) \in \mathbb{R}^+ \times \mathbb{R}^+$
Consumer-resource, Predator-prey: $f_v(u,v) \leq 0$, $g_u(u,v) \geq 0$ for $(u,v) \in \mathbb{R}^+ \times \mathbb{R}^+$

Constant solutions

If the steady state solution $(u_*(x), v_*(x)) \equiv (u_*, v_*)$, then the eigenvalue problem

$$\begin{cases} d_1\Delta\phi + f_u(u_*, v_*)\phi + f_v(u_*, v_*)\psi = \mu\phi, & x \in \Omega, \\ d_2\Delta\psi + g_u(u_*, v_*)\phi + g_v(u_*, v_*)\psi = \mu\psi, & x \in \Omega, \\ \nabla\phi \cdot n = \nabla\psi \cdot n = 0, & x \in \partial\Omega. \end{cases}$$

is solvable.

$$L\begin{pmatrix} \phi \\ \psi \end{pmatrix} = \begin{pmatrix} d_1\Delta\phi \\ d_2\Delta\psi \end{pmatrix} + \begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix}\begin{pmatrix} \phi \\ \psi \end{pmatrix}$$

Fourier series solution

$$\begin{pmatrix} \phi(x) \\ \psi(x) \end{pmatrix} = \sum_{j=0}^{\infty}\begin{pmatrix} a_j \\ b_j \end{pmatrix}\varphi_j(x).$$

where $0 = \mu_0 < \mu_1 \le \mu_2 \le \cdots \mu_j \to \infty$, and

$$\Delta\varphi_j(x) = -\mu_j\varphi_j(x), \quad x \in \Omega, \quad \nabla\varphi \cdot n = 0, \quad x \in \partial\Omega.$$

Reduction to matrix eigenvalues

$$L\begin{pmatrix}\phi\\ \psi\end{pmatrix}=\begin{pmatrix}d_1\Delta\phi\\ d_2\Delta\psi\end{pmatrix}+\begin{pmatrix}f_u & f_v\\ g_u & g_v\end{pmatrix}\begin{pmatrix}\phi\\ \psi\end{pmatrix}$$

From the uniqueness of Fourier expansion, we obtain

$$\sum_{j=0}^{\infty}\left(-\mu_j d_1 a_j + f_u a_j + f_v b_j - \mu a_j\right)\varphi_j = 0,$$

$$\sum_{j=0}^{\infty}\left(-\mu_j d_2 b_j + g_u a_j + g_v b_j - \mu b_j\right)\varphi_j = 0,$$

and (a_j, b_j) satisfies

$$L_j\begin{pmatrix}a_j\\ b_j\end{pmatrix}=\begin{pmatrix}-d_1\mu_j+f_u & f_v\\ g_u & -d_2\mu_j+g_v\end{pmatrix}=\lambda\begin{pmatrix}a_j\\ b_j\end{pmatrix}.$$

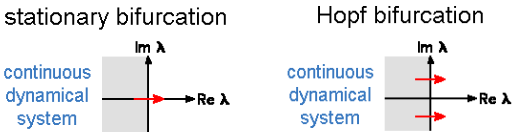
Theorem 6.1. If $L(\phi,\psi)=\mu(\phi,\psi)$, then there exists $j_i\in\mathbb{R}^N\cup\{0\}$ $(i=1,\cdots,k)$ such that $(\phi,\psi)=\sum_{i=1}^{k}(a_{j_i},b_{j_i})\varphi_{j_i}$ and $L_{j_i}(a_{j_i},b_{j_i})=\mu(a_{j_i},b_{j_i})$. In particular if $i=1$, then $(\phi,\psi)=(a_j,b_j)\varphi_j$ and $L_j(a_j,b_j)=\mu(a_j,b_j)$.

Stability of (u_*, v_*) w.r.t. R-D system

$$L_j \begin{pmatrix} a_j \\ b_j \end{pmatrix} = \begin{pmatrix} -d_1\mu_j + f_u & f_v \\ g_u & -d_2\mu_j + g_v \end{pmatrix} = \lambda \begin{pmatrix} a_j \\ b_j \end{pmatrix}.$$

$$T_j = Trace(L_j) := -(d_1 + d_2)\mu_j + f_u + g_v = -(d_1 + d_2)\mu_j + T_0,$$
$$D_j = Det(L_j) := d_1 d_2 \mu_j^2 - (d_1 g_v + d_2 f_u)\mu_j + f_u g_v - f_v g_u = d_1 d_2 \mu_j^2 - (d_1 g_v + d_2 f_u)\mu_j + D_0.$$

Stable with ODE: if $T_0 < 0$ and $D_0 > 0$
Stable with R.D. system: if $T_j < 0$ and $D_j > 0$ for all $j \in \mathbb{R}^N \cup \{0\}$, and unstable otherwise
$T_n = 0$: possible Hopf bifurcation occurs
$D_n = 0$: possible steady state bifurcation (pitchfork) occurs



When the stability is preserved

Let (u_*, v_*) be a constant steady state solution of the R.-D. system

$$\begin{cases} u_t = d_1 \Delta u + f(u,v), & x \in \Omega, \quad t > 0, \\ v_t = d_2 \Delta v + g(u,v), & x \in \Omega, \quad t > 0, \\ \nabla u \cdot n = \nabla v \cdot n = 0, & x \in \partial\Omega, \quad t > 0, \end{cases}$$

The corresponding ODE system is
$u_t = f(u,v), \quad v_t = g(u,v)$.

Theorem 6.2. If $d_1 = d_2 = d$, then the stability of (u_*, v_*) w.r.t. R.-D. system is same as the one w.r.t. ODE system.

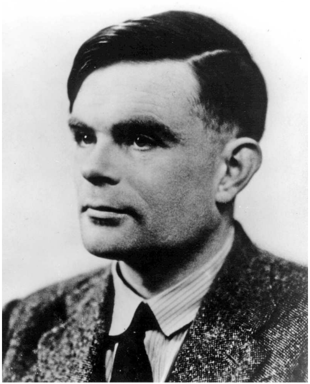
Proof: If λ is an eigenvalue of L_0, then $\lambda - d\mu_j$ is an eigenvalue of L_j.

Theorem 6.3. If (u_*, v_*) is stable w.r.t. ODE system, then there exists $M > 0$ such that when $d_1, d_2 > M$, then (u_*, v_*) is stable w.r.t. R.-D. system.

Proof: $T_j = Trace(L_j) = -(d_1 + d_2)\mu_j + f_u + g_v = -(d_1 + d_2)\mu_j + T_0 < 0$ if $T_0 < 0$.
$D_j = Det(L_j) = d_1 d_2 \mu_j^2 - (d_1 g_v + d_2 f_u)\mu_j + D_0 \geq M^2 \mu_j^2 - C_1 M \mu_j + D_0 =$
$M\mu_j(M\mu_j - C_1) + D_0 > 0$ if $M > C_1/\mu_1$ where $C_1 = |f_u| + |g_v|$.

Theorem 6.4. If (u_*, v_*) is stable w.r.t. ODE system, and the function
$D(p) = d_1 d_2 p^2 - (d_1 g_v + d_2 f_u)p + D_0 > 0$ for all $p \geq 0$, then (u_*, v_*) is stable w.r.t. R.-D. system.

Alan Turing (1912-1954)



THE CHEMICAL BASIS OF MORPHOGENESIS

BY A. M. TURING, F.R.S. *University of Manchester*

(*Received* 9 *November* 1951—*Revised* 15 *March* 1952)

It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by random disturbances. Such reaction-diffusion systems are considered in some detail in the case of an isolated ring of cells, a mathematically convenient, though biologically unusual system. The investigation is chiefly concerned with the onset of instability. It is found that there are six essentially different forms which this may take. In the most interesting form stationary waves appear on the ring. It is suggested that this might account, for instance, for the tentacle patterns on *Hydra* and for whorled leaves. A system of reactions and diffusion on a sphere is also considered. Such a system appears to account for gastrulation. Another reaction system in two dimensions gives rise to patterns reminiscent of dappling. It is also suggested that stationary waves in two dimensions could account for the phenomena of phyllotaxis.

The purpose of this paper is to discuss a possible mechanism by which the genes of a zygote may determine the anatomical structure of the resulting organism. The theory does not make any new hypotheses; it merely suggests that certain well-known physical laws are sufficient to account for many of the facts. The full understanding of the paper requires a good knowledge of mathematics, some biology, and some elementary chemistry. Since readers cannot be expected to be experts in all of these subjects, a number of elementary facts are explained, which can be found in text-books, but whose omission would make the paper difficult reading.

1. A MODEL OF THE EMBRYO. MORPHOGENS

In this section a mathematical model of the growing embryo will be described. This model will be a simplification and an idealization, and consequently a falsification. It is to be hoped that the features retained for discussion are those of greatest importance in the present state of knowledge.

The model takes two slightly different forms. In one of them the cell theory is recognized but the cells are idealized into geometrical points. In the other the matter of the organism is imagined as continuously distributed. The cells are not, however, completely ignored, for various physical and physico-chemical characteristics of the matter as a whole are assumed to have values appropriate to the cellular matter.

With either of the models one proceeds as with a physical theory and defines an entity called 'the state of the system'. One then describes how that state is to be determined from the state at a moment very shortly before. With either model the description of the state consists of two parts, the mechanical and the chemical. The mechanical part of the state describes the positions, masses, velocities and elastic properties of the cells, and the forces between them. In the continuous form of the theory essentially the same information is given in the form of the stress, velocity, density and elasticity of the matter. The chemical

[Turing, 1952] The Chemical Basis of Morphogenesis.
Phil. Trans. Royal Society London B

Turing instability

$$L_j \begin{pmatrix} a_j \\ b_j \end{pmatrix} = \begin{pmatrix} -d_1\mu_j + f_u & f_v \\ g_u & -d_2\mu_j + g_v \end{pmatrix} = \lambda \begin{pmatrix} a_j \\ b_j \end{pmatrix}.$$

$$T_j = Trace(L_j) := -(d_1 + d_2)\mu_j + f_u + g_v = -(d_1 + d_2)\mu_j + T_0,$$
$$D_j = Det(L_j) := d_1 d_2 \mu_j^2 - (d_1 g_v + d_2 f_u)\mu_j + f_u g_v - f_v g_u = d_1 d_2 \mu_j^2 - (d_1 g_v + d_2 f_u)\mu_j + D_0.$$

If (u_*, v_*) is stable w.r.t. ODE system, then $T_0 < 0$ and $D_0 > 0$.
For $j \geq 1$, $T_j = -(d_1 + d_2)\mu_j + f_u + g_v = -(d_1 + d_2)\mu_j + T_0 < 0$.
So for (u_*, v_*) to be unstable, we must have $D_j < 0$ for some $j \in \mathbb{R}^N$.

Then $d_1 g_v + d_2 f_u > 0$, f_u and g_v must be of different signs.
We assume that $\underline{f_u > 0}$ and $\underline{g_v < 0}$.

Solving $D_j = d_1 d_2 \mu_j^2 - (d_1 g_v + d_2 f_u)\mu_j + D_0 < 0$,
we obtain $0 < d_1 < \dfrac{d_2 f_u \mu_j - D_0}{\mu_j(d_2\mu_j - g_v)}$ or $d_2 > \dfrac{D_0 - d_1 g_v \mu_j}{\mu_j(f_u - d_1\mu_j)}$.

More stability

Let (u_*, v_*) be a constant steady state solution of the R.-D. system

$$\begin{cases} u_t = d_1 \Delta u + f(u,v), & x \in \Omega, \quad t > 0, \\ v_t = d_2 \Delta v + g(u,v), & x \in \Omega, \quad t > 0, \\ \nabla u \cdot n = \nabla v \cdot n = 0, & x \in \partial\Omega, \quad t > 0, \end{cases}$$

The corresponding ODE system is
$u_t = f(u,v), \quad v_t = g(u,v).$

Theorem 6.5. Suppose that (A) $f_u > 0$ (activator), $g_v < 0$ (inhibitor);
(B) $D_1 = f_u g_v - f_v g_u > 0$ and $f_u + g_v < 0$.

1. For fixed $d_2 > 0$, if $d_1 > \max_{j \in \mathbb{R}^N} \dfrac{d_2 f_u \mu_j - D_0}{\mu_j (d_2 \mu_j - g_v)}$, then (u_*, v_*) is stable w.r.t. R.-D. system.

2. For fixed $d_1 > 0$, if $0 < d_2 < \min_{j \in \mathbb{R}^N} \dfrac{D_0 - d_1 g_v \mu_j}{\mu_j (f_u - d_1 \mu_j)}$, then (u_*, v_*) is stable w.r.t. R.-D. system.

Note: 1. there are only finitely many $j \in \mathbb{R}^N$ such $\dfrac{D_0 - d_1 g_v \mu_j}{\mu_j (f_u - d_1 \mu_j)} > 0$.

2. there are infinitely many $j \in \mathbb{R}^N$ such that $\dfrac{d_2 f_u \mu_j - D_0}{\mu_j (d_2 \mu_j - g_v)} > 0$, but as $j \to \infty$,

$\dfrac{d_2 f_u \mu_j - D_0}{\mu_j (d_2 \mu_j - g_v)} \to 0.$

Turing Instability

Let (u_*, v_*) be a constant steady state solution of the R.-D. system

$$\begin{cases} u_t = d_1 \Delta u + f(u,v), & x \in \Omega, \quad t > 0, \\ v_t = d_2 \Delta v + g(u,v), & x \in \Omega, \quad t > 0, \\ \nabla u \cdot n = \nabla v \cdot n = 0, & x \in \partial\Omega, \quad t > 0, \end{cases}$$

The corresponding ODE system is
$u_t = f(u,v), \quad v_t = g(u,v)$.

Theorem 6.6. [Turing, 1952] Suppose that (A) $f_u > 0$ (activator), $g_v < 0$ (inhibitor); (B) $D_1 = f_u g_v - f_v g_u > 0$ and $f_u + g_v < 0$.

1. For fixed $d_2 > 0$, if $0 < d_1 < \max_{j \in \mathbb{R}^N} \dfrac{d_2 f_u \mu_j - D_0}{\mu_j (d_2 \mu_j - g_v)}$, then (u_*, v_*) is unstable w.r.t. R.-D. system.
2. For fixed $d_1 > 0$, if $d_2 > \min_{j \in \mathbb{R}^N} \dfrac{D_0 - d_1 g_v \mu_j}{\mu_j (f_u - d_1 \mu_j)}$, then (u_*, v_*) is unstable w.r.t. R.-D. system.

Turing instability can be caused by small d_1 and large d_2.
[Gierer-Meinhardt, 1972] short-range activator and long-range inhibitor causes Turing instability.

An artificial example

$$J = \begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix} = \begin{pmatrix} 2 & -4 \\ 2 & -3 \end{pmatrix}$$

For ODE, it is stable, since $T_0 = f_u + g_v = -1 < 0$ and $D_0 = f_u g_v - f_v g_u = 2 > 0$.
We also have $f_u = 2 > 0$ and $g_v = -3 < 0$.
Then when $d_2 > \min_{j \in \mathbb{R}^N} \dfrac{2 + 3d_1\mu_j}{\mu_j(2 - d_1\mu_j)}$, the Turing instability holds.

<u>Example</u>: $n = 1$, $\Omega = (0, \pi)$, $\mu_j = j^2$, $d_1 = 0.1$
Then for $j = 1, 2, 3, 4$, $\mu_j = 1, 4, 9, 16$, $d_2 > \min\left\{\frac{23}{19}, \frac{1}{2}, \frac{47}{99}, \frac{17}{16}\right\} = \frac{47}{99}$.
So the steady state loses the stability when $d_2 > 47/99$, and the corresponding eigen-mode is $j = 3$, or $\cos(3x)$.

When $d_2 = 0.5$, the matrix $L_3 = \begin{pmatrix} 2 - d_1\mu_3 & -4 \\ 2 & -3 - d_2\mu_3 \end{pmatrix} = \begin{pmatrix} 1.1 & -4 \\ 2 & -7.5 \end{pmatrix}$,
eigenvalue $\lambda_1 = -6.44$ (eigenvector $(0.47, 0.88)$), $\lambda_2 = 0.039$ (eigenvector $(0.97, 0.26)$)
So the solution is unstable like $(u(x,t), v(x,t)) = (u_*, v_*) + e^{0.039t}(0.97, 0.26)\cos(3x)$

Pattern formation matrix sign patterns

Condition for Turing instability:
(A) $f_u > 0$ (activator), $g_v < 0$ (inhibitor);
(B) $D_1 = f_u g_v - f_v g_u > 0$ and $f_u + g_v < 0$.

Activator-inhibitor type: $\begin{pmatrix} + & - \\ + & - \end{pmatrix}$

positive feedback type: $\begin{pmatrix} + & + \\ - & - \end{pmatrix}$

General definitions of stability

Let A be a real-valued $n \times n$ matrix, and let D be a real-valued $n \times n$ diagonal matrix $diag(d_1, d_2, \cdots, d_n)$. We will write $D \geq 0$ if all $d_i \geq 0$ and $D > 0$ if all $d_i > 0$.

1. A is stable if all eigenvalues of A have negative real part;
2. A is strongly stable with respect to diffusion if $A - D$ is stable for every diagonal matrix $D \geq 0$;
3. A is excitable with respect to diffusion if it is stable, but not strongly stable with respect to diffusion.
4. A is D-stable if DA stable for all $D > 0$.
5. A is Volterra-Lyapunov stable if there exists a $D > 0$ for which $AD + DA^T < 0$.

Lemma.
1. If A is Volterra-Lyapunov stable, then A is both strongly stable and D-stable.
2. If A is a normal matrix ($AA^T = A^T A$) and stable, then A is Volterra-Lyapunov stable. (See [Cross, 1978, LAA])

In the definition of "strongly stable with respect to diffusion", D can also be replaced by any $D \geq 0$ if we also consider the effect of cross-diffusion.

More Definitions

1. A submatrix of a matrix is called a principal submatrix if rows and columns with the same indices are deleted.
2. The determinant of a submatrix is called a minor, thus the determinant of a principal submatrix is a principal minor.
3. If $I \subset \{1, 2, \cdots, n\}$ is a subset of indices, then $\det A[I]$ denotes the corresponding principal minor, which is formed by the rows and columns with indices in I. The quantity $(-1)^{|I|}\det A[I]$ where $|I|$ is the number of indices in I is called the signed principal minor.
4. $I^c = \{1, 2, \cdots, n\} - I$ is the complement of I.

Determinant formula: if D is diagonal

$$\det(A - D) = \sum_{k=0}^{n}(-1)^k \sum_{|I|=k}\left(\det A(I) \prod_{i\in I^c} d_i\right)$$
$$= \det A + \sum_{k=1}^{n-1}(-1)^k \sum_{|I|=k}\left(\det A(I) \prod_{i\in I^c} d_i\right) + (-1)^n \prod_{i=1}^{n} d_i.$$

Results

Theorem 1. [Cross, 1978, LAA] If A is strongly stable with respect to diffusion (or D-stable), then all signed principal minors of A are all non-negative, with at least one of each order positive.

Theorem 2. [Cross, 1978, LAA] [Wang-Li, 2001, JMAA] If $n = 2$ or $n = 3$, A is stable and all signed principal minors of A are all non-negative with at least one of each order positive, then A is strongly stable with respect to diffusion. (For $n = 2$, also D-stable.)

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Theorem 3. [Satnoianu-van den Driessche, 2005, LAA] When $n = 4$, there is an example of A which is stable and all signed principal minors of A are all non-negative with at least one of each order positive, and A is not strongly stable with respect to diffusion.

$$A = \begin{pmatrix} -0.001 & -0.0007 & -0.0007 & -0.0028 \\ 0.004 & -0.001 & -0.0007 & -0.0028 \\ 0.004 & 0.004 & -0.001 & -0.0028 \\ -1 & -1 & -1 & -4 \end{pmatrix}$$

$D = diag(0, 0, 0, 1)$.
Eigenvalues of A: -4.0021, $-0.0003484 \pm 0.0000996i$, -0.0002055 (stable)
Eigenvalues of $A - D$: -5.0017, $0.0000495 \pm 0.0016237i$, -0.0014204 (unstable)
one can check all signed principal minors of A are all positive

Therefore for $A - kD$, there exists $k \in (0, 1)$ such that a Hopf bifurcation occurs (with eigenvalues $\pm\omega i$).

Results

Theorem 4. [Satnoianu-van den Driessche, 2005, LAA] For every diagonal matrix $D \geq 0$, $sign(\det(A - D)) = (-1)^n$, so if A is stable, then $\det(A - D) \neq 0$ and $A - D$ cannot have a zero eigenvalue.

Theorem 5. [Wang-Li, 2001, JMAA] If A is stable but at least one signed principal minor is negative, then there exists $D \geq 0$ such that $A - D$ is unstable. (So A is excitable)
In this case, $\det(A - D) = 0$ so zero is an eigenvalue.

Summary for bifurcations

1. Stable means eigenvalue $\lambda < 0$.
2. Two routes from stable to unstable: (i) $\lambda = 0$ ($\det(A - D) = 0$) steady state bifurcation; (ii) $\lambda = \pm\beta i$ Hopf bifurcation.
3. A has a steady state bifurcation for some $D \geq 0$ *if and only if* at least one signed principal minor is negative.
4. A can have a Hopf bifurcation even when all signed principal minors are positive. (example when $n = 4$)

Questions:

1. What is a necessary and sufficient condition for A to have a Hopf bifurcation for some $D \geq 0$? That is, A is stable, but $A - D$ has a pair of purely imaginary eigenvalues. ($n = 2$: impossible; $n = 3$: [Anma-Sakamoto, 2012, Kodai Math J]?)
2. What sign pattern of A makes Hopf bifurcation possible?

Detecting Hopf bifurcation

[Bodine-Deaett-McDonald-Olesky-van den Driessche, 2012, LAA]
[Garnett-Olesky-van den Driessche, 2013, EJLA]
[Culos-Olesky-van den Driessche, 2016, JMB]

1. An $n \times n$ sign pattern is an $n \times n$ matrix with entries from $\{+, -, 0\}$. So the sign pattern of a real matrix $A = [a_{ij}]$ is the sign pattern $\mathcal{A} = sgn(A) = [sgn(a_{ij})]$; the matrix A is called a realization of $\mathcal{A}$. The sign pattern class $Q(\mathcal{A})$ of the sign pattern $\mathcal{A}$ is the set $Q(\mathcal{A}) = \{A : sgn(A) = \mathcal{A}\}$. A sign pattern $\mathcal{A}' = [\alpha'_{ij}]$ is a superpattern of $\mathcal{A}$ if $\alpha'_{ij} = \alpha_{ij}$ for all $\alpha_{ij} \neq 0$.
2. The digraph $D(\mathcal{A})$ of a sign pattern $\mathcal{A} = [\alpha_{ij}]$ has n vertices, an arc from i to j if $\alpha_{ij} \neq 0$ and a loop at vertex i if $\alpha_{ii} \neq 0$. The signed digraph of sign pattern $\mathcal{A}$ is the digraph of $\mathcal{A}$ with α_{ij} on the arc from i to j if $\alpha_{ij} \neq 0$ and α_{ii} on the loop at vertex i if $\alpha_{ii} \neq 0$.
3. The refined inertia $ri(A)$ of a real $n \times n$ matrix A is the ordered 4-tuple $(n_+, n_-, n_z, 2n_p)$ such that n_+ (resp., n_-) is the number of eigenvalues (including multiplicities) of A with positive (resp., negative) real part, and n_z (resp., $2n_p$) is the number of zero eigenvalues (resp., nonzero pure imaginary eigenvalues) of A. Here $n_+ + n_- + n_z + 2n_p = n$.
4. The refined inertia $ri(\mathcal{A})$ of a sign pattern is $ri(\mathcal{A}) = \{ri(A) : A \in Q(\mathcal{A})\}$.
5. A matrix A is stable if $ri(A) = (0, n, 0, 0)$.

Detecting Hopf bifurcation

1. A sign pattern $\mathcal{A}$ is sign nonsingular (SNS) if $n_z = 0$ (i.e., $\det(A) \neq 0$) for all $A \in Q(\mathcal{A})$.
2. $\mathcal{A}$ of order n is sign stable if $n_- = n$ for all $A \in Q(\mathcal{A})$.
3. $\mathcal{A}$ is potentially stable if $n_- = n$ for some $A \in Q(\mathcal{A})$.
4. If the refined inertia of $\mathcal{A}$ contains all possible refined inertias for its order, then $\mathcal{A}$ is refined inertially arbitrary.
5. If any given multiset of n numbers that is closed under complex conjugation is the spectrum of some $n \times n$ matrix $A \in Q(\mathcal{A})$, then $\mathcal{A}$ is spectrally arbitrary.
6. Hopf bifurcation usually occurs with refined inertia changing from $(0, n, 0, 0)$ to $(0, n-2, 0, 2)$ to $(2, n-2, 0, 0)$.
7. For $n \geq 2$, let $\mathbb{H}_n = \{(0, n, 0, 0), (0, n-2, 0, 2), (2, n-2, 0, 0)\}$. A sign pattern $\mathcal{A}_n$ requires refined inertia $\mathbb{H}_n$ if $\mathbb{H}_n = ri(\mathcal{A}_n)$, and $\mathcal{A}_n$ allows refined inertia $\mathbb{H}_n$ if $\mathbb{H}_n \subseteq ri(\mathcal{A}_n)$.

$n = 2, 3, 4$

[Bodine-Deaett-McDonald-Olesky-van den Driessche, 2012, LAA]
[Olesky-Rempel-van den Driessche, 2013, Involve]

1. For $n = 2$, no sign pattern requires $\mathbb{H}_2$, but there is one allows $\mathbb{H}_2$ (it is spectrally arbitrary).
2. For $n = 3$, Up to equivalence, there are 8 sign patterns that require $\mathbb{H}_3$.
3. For $n = 4$, tree sign patterns are classified.
4. Conjecture: no $n \times n$ sign pattern requires $\mathbb{H}_n$ for $n \geq 8$. (an example of 7×7 sign pattern that require $\mathbb{H}_7$ is known.)