A dynamical systems approach to actin-based motility in Listeria monocytogenes

S. Hotton

Department of Organismic and Evolutionary Biology, Harvard University - Cambridge, MA 02138, USA

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Abstract – A simple kinematic model for the trajectories of Listeria monocytogenes is generalized to a dynamical system rich enough to exhibit the resonant Hopf bifurcation structure of excitable media and simple enough to be studied geometrically. It is shown how L. monocytogenes trajectories and meandering spiral waves are organized by the same type of attracting set.

Introduction. – Listeria monocytogenes is a widely distributed pathogenic bacterium which occasionally causes serious illness in humans. L. monocytogenes evades the host’s immune system by living inside its cells. Proteins located on the surface of the rod-shaped bacteria catalyze the polymerization of the infected cells’ actin molecules and this activity propels the bacteria through the cytoplasm [1]. The underlying mechanism of actin-based motility is a subject of great interest both because L. monocytogenes is a deadly pathogen and because actin filament assembly plays a role in many forms of cell movement [2]. A useful feature of actin-based motility in L. monocytogenes is the “comet tail” of actin filaments which are left behind as a cell is transported [3]. The “comet tails” provide a record of bacterial trajectories in the cytoplasm. These trajectories, which vary considerably between individuals, can be complicated and orderly at the same time. In the present work it is shown how these trajectories can be explained with a dynamical system that has a well known type of attracting set. The presence of this attracting set can account for the renewal of actin-based motility after the bacterium divides and the persistence of motility as the bacterium invades neighboring host cells.

L. monocytogenes trajectories are the result of a complicated interaction of proteins in a host cell’s cytoplasm or in a cytoplasmic extract [4]. There has been extensive research into the molecular mechanism underlying actin-based motility but they do not account for the complicated forms of L. monocytogenes’ actin comet tails [5–12]. In [13] Shenoy et al. present a simple and remarkably effective kinematic model for the trajectories of L. monocytogenes in a thin layer of cytoplasmic extract.

In the Shenoy et al. model the effect of actin polymerization is assumed to produce a net force on the cell body which points slightly off center and which causes the bacteria to spin about its long axis as it travels in two dimensions. The bacterium’s velocity is given by a vector whose direction varies sinusoidally with time and whose magnitude is fixed. Choosing units of measure so the speed is 1, letting $s$ stand for arc length, and $\theta$ stand for the velocity’s direction the Shenoy et al. model, in a non-dimensionalized form, is $d\theta/ds = \Omega \cos(s)$ where $\Omega \geq 0$ represents the maximum deflection from forward motion.

Since $d\theta/ds$ equals curvature the non-dimensionalized form of the Shenoy et al. model gives a one-parameter family of intrinsic equations for planar curves (i.e. a two-dimensional analog for the Frenet-Serret equations) which exhibit qualitative changes as the parameter $\Omega$ is varied. Shenoy et al. show that for small $\Omega$ the curve is sinusoidal, for $\Omega \approx 2.5$ it resembles a figure eight, and for larger values of $\Omega$ the curve tends to turn successively clockwise and counter-clockwise around a sequence of points (fig. 1). There are many qualitatively different types of curves for values of $\Omega$ from 0 to 16 and Shenoy et al. show that L. monocytogenes display most if not all of these types.

Although this kinematic model can reproduce many of the complicated L. monocytogenes trajectories it does not explain how the forces on the cell body arise or address the stability of the motion. The question of how actin-based motility arises is important because the bacteria have to divide in order to proliferate inside
the host organism and after cell division the protein catalyzing actin polymerization is redistributed on the bacterial surface [14,15]. The issue of stability is important because one of the functions served by actin-based motility is to enable L. monocytogenes to create “pseudopodal projections” from one host cell into another and thus allow the bacteria to avoid the host’s immune system [1]. If the dynamics underlying actin-based motility was not stable then obstacles in the bacteria’s path could disrupt the bacteria’s entry into the neighboring host cell. In the next section the model of Shenoy et al. is extended to allow the angular displacement of L. monocytogenes trajectories to accumulate. The third section explains how this extension leads to a dynamical system with the same type of attracting set as seen with meandering spiral waves. The fourth section shows how the existence of the attracting set accounts for actin-based motility developing and persisting in L. monocytogenes.

Generalizing the kinematic model. — It is well known in ballistics that it is difficult for a projectile to travel in a perfectly straight direction. For a self-propelled bacterium in a viscous medium even a small asymmetry in the cell body can cause it to eventually deviate from a straight course [16]. On the other hand, in the Shenoy et al. model the angular displacement remains within fixed bounds along the entire length of the curve and the overall trajectory conforms to a straight line despite the small scale oscillations in its direction. To improve the accuracy of the kinematic model it is worth considering previous studies on actin-based motility. Rutenberg and Grant [17] related the overall curvature of the trajectories to the number of randomly located actin filaments propelling the cell. They treated the torque produced by the filaments as a constant for relatively long periods of time which led to trajectories with constant curvature, \( d\theta/ds = \kappa \). For trajectories with \( \kappa \neq 0 \) starting in the direction \( \theta_0 = 0 \) the angular displacement grows in proportion to arc length.

Evidence for the secular dependence of angular displacement on arc length in the Rutenberg and Grant model was subsequently presented in the extensive experimental study on actin-based motility in L. monocytogenes [18]. The study found bacteria trajectories that were nearly circular and whose angular displacements and path lengths were nearly proportional to the elapsed time. Consequently, the angular displacements were nearly proportional to arc length.

Here we combine the approaches of Shenoy et al. and Rutenberg and Grant into a single model and present a summary of the types of paths this model displays. The Shenoy-Rutenberg model is, in non-dimensional form, \( d\theta/ds = \kappa + \Omega \cos(s) \) where \( \Omega, \kappa \) are constants. For small \( \kappa \) the paths are qualitatively the same as for \( \kappa = 0 \) but they veer from a straight course (as indicated by the dotted curves). The region of parameter space shown here only contains a portion of the parameter values that can replicate L. monocytogenes trajectories.

Evidence for these secular dependence of angular displacement on arc length cannot be evaluated in terms of elementary functions the curves are symmetrical and made up of congruent copies of an arc of length \( \pi \). Since the \((x, y)\) curve is invariant under reflection about the \(y\)-axis we can reflect the arc for \( 0 \leq s \leq \pi \) to obtain the arc for \(-\pi \leq s \leq \pi \).
For non-integral \( \kappa \) let \( r = \cot(\pi \kappa)x(\pi) + y(\pi) \). It can be shown that

\[
\begin{pmatrix}
x(s + 2\pi) \\
y(s + 2\pi) - r
\end{pmatrix} = \begin{pmatrix}
\cos(2\pi \kappa) - \sin(2\pi \kappa) \\
\sin(2\pi \kappa) \cos(2\pi \kappa)
\end{pmatrix} \begin{pmatrix}
x(s) \\
y(s) - r
\end{pmatrix}.
\]

From this it follows that the \((x, y)\) curve can be obtained by iteratively rotating the arc for \(-\pi \leq s \leq \pi\) about the point \((0, r)\) which is the center of symmetry for the figure.

For non-integral rational \( \kappa = p/q \) \((p, q \text{ coprime})\) and \( \Omega \neq 0 \) the \((x, y)\) curve is closed with \( q \)-fold rotational symmetry. It is the union of \( 2q \) congruent arcs of length \( \pi \). For irrational \( \kappa \) and \( \Omega \neq 0 \) the \((x, y)\) curve is quasiperiodic in the plane. It is the union of an infinite number congruent arcs with length \( \pi \).

For integer values of \( \kappa \) we can think of \( r \) as having gone to infinity. It can be shown that \( y(s + 2\pi) = y(s) \).

To express the value of \( x \) at multiples of \( \pi \) we can use the integral representation for Bessel functions

\[ J_\kappa(-\Omega) = \frac{1}{\pi} \int_0^\pi \cos(\kappa \sigma + \Omega \sin(\sigma)) \, d\sigma \]  

(this integral representation does not apply to non-integer values of \( \kappa \)). From this it follows that the \((x, y)\) curve can be obtained by iteratively translating the arc for \(-\pi \leq s \leq \pi\) horizontally by the distance \( 2\pi J_\kappa(-\Omega) \). When \(-\Omega\) is a zero of \( J_\kappa \) the \((x, y)\) curve is closed with length \( 2\pi \). Otherwise the \((x, y)\) curve is the union of an infinite sequence of congruent arcs with length \( \pi \). This generalizes a similar result from [13] for the \( \kappa = 0 \) case.

The points of maximal curvature on an \((x, y)\) curve occur where \( s \) is an even multiple of \( \pi \), the points of minimal curvature occur where \( s \) is an odd multiple of \( \pi \), and the curvature varies monotonically in between. In a neighborhood of \((0, 0)\) an arc of the \((x, y)\) curve lies above the horizontal tangent at \((0, 0)\) and for \( \kappa > \Omega \) the curvature is positive everywhere.

For \( 1 < \kappa > \Omega \) the \((x, y)\) curve has the form of a trochoi with its “petals” lying in a row (fig. 2). For small \( \Omega \) and \( 0 < \kappa < 1 \) the \((x, y)\) curve has the form of a hypotrochoid with its “petals” on the outside. For small \( \Omega \) and \( 1 < \kappa < 2 \) the \((x, y)\) curve has the form of an epitrochoid with its “petals” on the inside.

Flower-like curves such as these are traced out by the tips of spiral waves propagating through excitable media. Spiral waves occur in diverse systems with very different underlying mechanisms. This includes aggregating myxobacteria which form macroscopic waves as cells glide across a two-dimensional surface [20]. A spiral wave often propagates as though it were a rigid body rotating about a quiescent core. Away from the core the shape of the wave front converges to an Archimedean spiral [21,22]. However under appropriate circumstances the inner tip undergoes a secondary oscillation as the wave rotates and thereby traces a hypo/epi/trochoi-like curve. Spiral tip meander has been observed in many systems such as the BZ chemical reaction [23], heart tissue [24], and aggregating cells of Dictyostelium discoideum (cellular slime molds) [25].

Resonant Hopf bifurcations. – An important step toward understanding why spiral tip meander occurs in systems with such different underlying mechanisms was made by Barkley [28–30] who recognized, through numerical and mathematical analysis, the important role played by the group of orientation preserving congruences of the Euclidean plane, \( SE(2) \), and that this role can be exemplified by reducing the dynamics to five dimensions. The mathematics of Barkley’s breakthrough has been further elaborated and generalized [31–35]. Barkley’s approach can be nicely illustrated with the Shenoy-Rutenberg model since it already has the form of an intrinsic equation for planar curves. To do this we couple the Shenoy-Rutenberg model to a two-dimensional system from [36]. We write the Cartesian coordinates for this subsystem as \((X, Y)\).

The full differential equation is

\[ x' = \cos(\theta), \]
\[ y' = \sin(\theta), \]
\[ \theta' = \kappa + X, \]
\[ X' = -Y + (\mu - X^2 - Y^2)X, \]
\[ Y' = X + (\mu - X^2 - Y^2)Y, \]

where the parameter \( \mu \) corresponds to Barkley’s normalized bifurcation parameter [29]. For \( \mu < 0 \) the origin of the
(X, Y) subsystem is an attracting fixed point. At \( \mu = 0 \) the Hopf bifurcation occurs and for \( \mu > 0 \) there is an attracting circular limit cycle centered at the origin with radius \( \sqrt{\mu} \).

To concisely express the initial conditions we set \( \Omega = 0 \) for \( \mu < 0 \) and \( \Omega = \sqrt{\mu} \) for \( \mu > 0 \). For the initial condition \( (x, y, \theta, X, Y) = (0, 0, 0, \Omega, 0) \) the solution to the \((X, Y)\) subsystem is \( (X(s), Y(s)) = \Omega (\cos(s), \sin(s)) \) which gives \( \theta' = k + \Omega \cos(s) \) which in turn recovers eq. (1) for the \((x, y)\) subsystem.

A purely rotating spiral wave appears motionless in a frame rotating with it. The transition to meandering corresponds to the Hopf bifurcation. After the bifurcation the spiral tip appears in the rotating frame to trace a circularly shaped path although far from the core the wave continues to appear motionless.

By converting eq. (4) to a rotating coordinate system \((0, 0, 0, 0, 0)\) becomes a fixed point with spectrum \( \{\pm i k, 0, \mu \pm i \} \). The eigenvalues \( \pm i k \) arise from the translational symmetry of the plane and \( 0 \) arises from the rotational symmetry of the plane. At the Hopf bifurcation all five eigenvalues lie on the imaginary axis.

Barkley showed that the type of curve traced by a spiral tip in the stationary frame depends on where the Hopf eigenvalues cross the imaginary axis in relation to the translational eigenvalues. When the translational eigenvalues are between the Hopf eigenvalues the spiral tip will follow a hypotrochoid-like curve \((0 < k < 1 \text{ in eq. (4)})\). When the translational eigenvalues are outside of the Hopf eigenvalues \((k > 1 \text{ or } k < -1 \text{ in eq. (4)})\) the spiral tip will follow an epitrochoid-like curve \((1 < k < 2 \text{ in eq. (4)})\). When the translational eigenvalues \( k = 1 \text{ in eq. (4)} \).

In terms of \( L. \text{ monocytogenes} \) we can interpret \((X, Y)\) as the projection of the cell’s translational velocity to a plane orthogonal to the cell body’s long axis and we can interpret the oscillation of \((X, Y)\) as the effect of the cell’s spin on its propulsion system. The long axis and the \( X \) component are parallel to the surface being traversed while the \( Y \) component points in the orthogonal direction. For a cell constrained in two dimensions the \( Y \) component does not contribute to the motion. For \( \Omega = 0 \) the cell appears motionless in a frame rotating with it. For small \( \Omega > 0 \) the cell appears to follow a circularly shaped path in the rotating frame.

The detailed mechanisms behind spiral meander and \( L. \text{ monocytogenes} \) motility are different but the paths they follow are both part of a larger two-parameter family of curves. The paths followed by spiral-wave tips are organized around a first-order resonant Hopf bifurcation for which the translational and Hopf eigenvalues coincide \((k = 1 \text{ in eq. (4)})\). The paths followed by \( L. \text{ monocytogenes} \) are organized around a zero-order resonant Hopf bifurcation for which the translational and rotational eigenvalues coincide \((k = 0 \text{ in eq. (4)})\).

**The dynamics of \( L. \text{ monocytogenes} \) motility.** – Spiral waves appear in excitable media when, in the state space for the medium, the state is sufficiently close to the appropriate attracting set. Each state in the attracting set corresponds to a well formed spiral wave in the medium. In many cases there is a characteristic wavelength to the limiting form of the spiral wave [37]. In some cases any two spiral waves in a planar homogenous isotropic medium will be congruent. For media which support non-meandering spiral waves the attracting set is essentially a copy of the symmetry group \( \text{SE}(2) \). This is the type of attracting set the solutions to eq. (4) have when \( \mu < 0 \). The orbits of the dynamical system inside the attracting set are simple closed curves and thus bounded. These orbits correspond to spiral waves undergoing a pure rotation or \( L. \text{ monocytogenes} \) following a circular trajectory.

Aside from numerical simulations it is difficult to prepare excitable media so that the initial state of the system is within the attracting set, i.e. so that the medium begins with a well formed spiral wave which then undergoes a pure rotation. A purely rotating spiral wave only appears after a transient period. One way for a purely rotating spiral wave to appear is by disrupting a circular or linear wave front with an obstacle in the medium. The broken end of the wave front will then curl up and over time the shape of the wave will develop into a well formed spiral which propagates in a purely rotational manner. The disruption of a wave front by an obstacle brings the state of the system sufficiently close to the attracting set that it converges towards it.

For homogeneous isotropic excitable media which support meandering spiral waves the attracting set has another dimension. This is the type of attracting set the solutions to eq. (4) have when \( \mu > 0 \). Each point in the attracting set gives the position and orientation of the spiral wave as well as its phase within the period of meander. The orbits of the dynamical system inside the attracting set are bounded unless there is a resonance between the rotation of the spiral wave and the oscillation of the tip in which case they are unbounded. Meandering spiral waves appear after a transient period once the state of the system has been brought sufficiently close to the attracting set. For systems at or near resonance the core of the spiral wave will be transported across large distances.

Biological systems repeat many of the same developmental strategies in various contexts to form functional patterns. The presence of low-dimensional attracting sets in complicated dynamical systems can provide stability to developmental processes which are exposed to the environment. For instance there are prokaryotes (e.g. myxobacteria) and eukaryotes (e.g. \( D. \text{ discoideum} \)) which use spiral-wave dynamics to get individual cells dispersed over a wide area to aggregate together and develop multicellular reproductive organs. The underlying mechanisms by which myxobacteria and \( D. \text{ discoideum} \) move and communicate are quite different but the presence of an...
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attracting set for spiral-wave dynamics can allow the aggregation process to proceed despite the vagaries of their environments.

There has been a long running and continuing effort to determine the underlying mechanism responsible for the formation of actin-based motility [5–12,38]. The Shenoy et al. model is effective at duplicating *L. monocytogenes* trajectories but it is not directly based on a physico-chemical mechanism. Their model proceeds from general considerations about how the forces produced by actin polymerization must act on the cell. In order for the cell to change direction as it moves there must be some asymmetry in the distribution of forces exerted on the cell surface. By treating the net propulsive force as a constant parallel to the long axis of the cell and whose exertion point rotates at a constant distance about the long axis the magnitude of the component of the net torque orthogonal to the plane of motion varies in a precisely sinusoidal fashion. In this way the cell body oscillates about its center of mass much like an ideal torsional spring. With the propulsive force always parallel to the long axis the cell moves in trajectories that alternately wind clockwise and counter-clockwise.

However, this clockwork-like mechanism does not simply appear fully formed. For *L. monocytogenes* engaged in actin-based motility the concentration of ActA (the catalyst for actin polymerization on *L. monocytogenes*) along the cell wall increases from the apical pole to the basal pole. *L. monocytogenes* cells reproduce by dividing along a septum midway between the poles. After division each daughter cell forms a new apical pole at the septation region and ActA concentration is redistributed along the cell wall [14,15].

When a *L. monocytogenes* cell first begins moving it engages in a “hopping”-type motion. The density of actin builds up behind the basal pole until there is a sudden acceleration of the cell. The actin tail then becomes rarefied, the cell subsequently decelerates nearly to rest, and the cycle repeats. After several cycles the cell eventually settles down to a relatively constant speed [7,16].

One function served by the actin-based motility of *L. monocytogenes* is the transport of bacteria from one host cell to another without the bacteria having to leave the confines of the host cells. This is accomplished when a bacterium presses against the host’s plasma membrane to create a “pseudopodal projection” with the bacterium inside. The bacterium enters a neighboring host cell when the pseudopodal projection is phagocytosed by the neighboring cell [1].

During the transient period *L. monocytogenes* movement is sensitive to obstacles in its environment but it becomes more robust when it reaches a steady speed [16]. The presence of a low-dimensional attracting set for actin-based motility can provide stability in the development of *L. monocytogenes* infectiousness. When the state of the system is in its transient phase, away from the attracting set, obstacles in the environment can have the effect of perturbing the system from one orbit to another with a very different course. On the other hand when the state of the system is close to the attracting set it can quickly return to the attracting set after an obstacle causes a perturbation. This accounts for how *L. monocytogenes* motility can persist as it forms a pseudopodal projection.

Moreover the attracting set for actin-based motility by *L. monocytogenes* confined to two dimensions appears to be of the same type as for spiral tip meander in two dimensions. In both cases the points of the attractor correspond to the position, the orientation, and the phase in the secondary oscillation of the object that is moving. For the purposes of transport it is useful for the system to be near a resonance. The Shenoy et al. model corresponds to a zero-order resonance which helps account for its effectiveness although the model needs to be placed in a larger mathematical context to see this and to account for how actin-based motility in *L. monocytogenes* arises and persists in the presence of obstacles.

**Conclusion.** – Spiral waves involve the cooperative behavior of multiple agents while a bacterium is generally thought of as a single agent. However this apparent association of the first-order resonant Hopf bifurcation to the organized motion of multiple agents and the zero-order resonant Hopf bifurcation to the motion of a single agent is not a general principal. The movement of an individual bacterium can be regarded as the action of a single agent but actin-based motility involves the polymerization of actin so it can also be regarded as an organized activity involving many chemical agents. Inert beads coated with proteins which catalyze actin polymerization can also engage in actin-based motility [39,40].

Actin is an important constituent of the cytoskeletons of eukaryotic cells and it forms locomotory structures such as filopodia in which actin organizes into bundles and lamelipodia in which actin organizes into meshworks [41–47]. Numerical simulations indicate that actin can also form spiral waves [48] and there is evidence for actin forming spiral waves inside of *D. discoideum* pseudopodia [49,50].

The actin-rich cytoplasm of eukaryotic cells can be seen as a type of excitable media with a propensity to locomotory behavior which several pathogens, in addition to *L. monocytogenes*, have evolved to take advantage of in order to transport themselves. Actin-based motility occurs with the bacteria *Shigella flexneri* [51], species of *Rickettsia* bacteria [52], and vacciniavirus particles [53]. The detailed mechanism of actin-based motility varies between these pathogens but they each involve catalyzing the polymerization of actin, [54–56].

When *L. monocytogenes* bacteria are constrained to move in two dimensions their trajectories can form a complicated series of coils. As with the trajectories of meandering spiral waves, the trajectories of *L. monocytogenes* are composed of essentially congruent copies of a finite curve repeatedly joined end to end. The form of the repeating unit appears after a transient period.
and it varies between different occurrences of meandering spiral waves and between different individual *L. monocytogenes*. Yet complicated curves characteristic of both types of phenomena can be replicated using a two-parameter family of dynamical systems with the same type of attracting set as eq. (4). Taken together these lines of evidence support the idea that actin-based motility in *L. monocytogenes* is organized by the same type of low-dimensional attracting set that organizes spiral tip meander.

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