Biological version of Braess' paradox arising from perturbed homeostasis

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Braess' paradox is an observation in traffic networks in which changes to the structure of the network—such as the addition of a road—which are intended to enhance flow can often instead have the paradoxical effect of reducing flow through the network. Versions of Braess' paradox have subsequently been observed in many other network types. Homeostasis is a seemingly unrelated biological concept in which interacting regulatory mechanisms work in concert to regulate a particular system output such that it is relatively insensitive to changes in input. A classic example is the broad range of ambient temperatures (input) over which mammalian body temperature (output) is close to constant. In this work, we propose a connection between these concepts using the mathematical formulation of infinitesimal homeostasis and argue that perturbations of homeostatic systems in disease may often lead to observations of paradoxical behavior via the universal unfoldings of infinitesimal homeostasis. We illustrate the concept with an example system drawn from the study of the pathophysiology and treatment of asthma; as a network flow model, this exhibits a form of paradoxical behavior akin to Braess' paradox which we argue arises from perturbation of homeostasis due to disease.

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I. INTRODUCTION

Homeostasis is a biological notion in which interdependent processes interact to maintain a relatively stable equilibrium which resists input perturbations. One classic example is the mammalian regulation of body temperature, which is insensitive to ambient temperature over a relatively wide range. Homeostatic regulation is thought to be important in many areas of the life sciences, ranging from body temperature [1] to gene regulatory networks [2] and many more.

Braess' paradox is an observed phenomenon in congested traffic networks wherein alterations to the network which are meant to improve traffic flow instead result in worsening of conditions overall, or, conversely, that road closures which might be expected to impede traffic flow instead result in overall improvement [3–5]. In the context of game theory, Braess' paradox can be described in terms of Nash equilibria: Namely, that while no driver has an incentive to change their strategy unilaterally, the overall result is not globally optimal [6]. In addition to classic traffic flow examples [7,8], the more general notion—that noncooperative local optimization may not achieve a global optimum—has led to other versions of Braess' paradox in diverse fields ranging from mesoscopic networks [9] to biological systems such as metabolic networks [10].

We argue that there is a connection between homeostasis and a biological version of Braess' paradox which can be understood using the notion of perturbed infinitesimal homeostasis. This theory was developed to understand the emergence of homeostasis in mathematical models of biological processes [2,11,12]. As we will show, one consequence is that perturbations away from homeostasis might be expected to generate seemingly paradoxical behavior in some circumstances.

We use an example from lung physiology, in particular the behavior of the lung in asthma, to illustrate the connection. Several seemingly disjoint paradoxical responses have been observed in studies of the pathophysiology of asthma [13–21]. We demonstrate that perturbations of biologically homeostatic systems can exhibit these paradoxical responses, which can be viewed as a form of Braess' paradox in terms of transitions between network flow configurations.

II. MODEL

A. Infinitesimal homeostasis

The notion of homeostasis in biological systems is that organisms self-regulate, via interacting regulatory processes, to maintain relatively stable equilibria over a range of differing inputs. In addition to the classic example of body temperature [1], other processes are thought to be homeostatic, for example, blood pressure regulation [22], glucose regulation [23], and many others [24–26]. A typical schematic is given in Fig. 1, showing the region of relative stability with near-constant function (output) over a wider range of stimulus (input).

The biological notion of homeostasis can be formalized using the concept of *infinitesimal homeostasis*, the idea being that regions of homeostasis will be expected to emerge via certain geometric structures (in terms of the stable equilibrium as a function of the input parameter). Here, we give a brief overview of the theory and, as part of that, describe some structures through which infinitesimal homoeostasis might arise; for more complete details, the reader is referred to Refs. [2,11,12].

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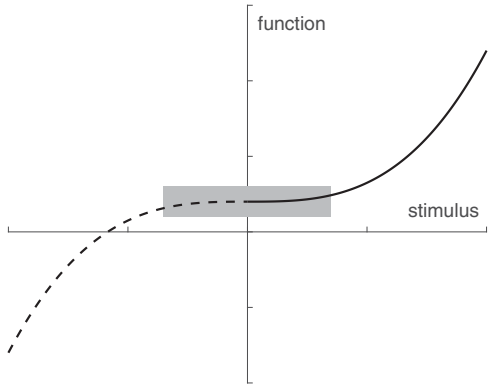

FIG. 1. Schematic illustration of homeostasis showing relative stability with near constant function (output) over a wider range of stimulus (input). Dashed line indicates the extension for "negative" stimulus.

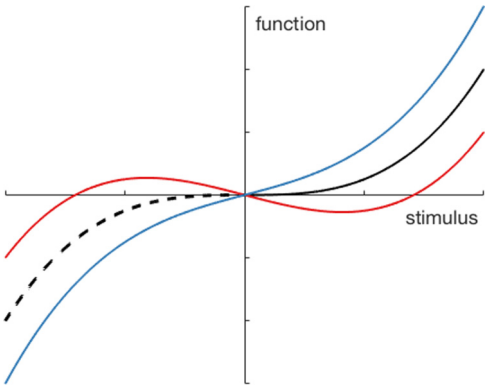

FIG. 2. Unfolding of infinitesimal homeostasis (black, chair homeostasis $Y = \hat{p}^3$; blue, $\hat{q} = +\delta$ perturbation; red, $\hat{q} = -\delta$ perturbation). Note that the $\hat{q} = -\delta$ perturbation (red curve) exhibits local extrema while the others are monotonic.

Consider a (biological) system modeled by a system of first-order ordinary differential equations

$$x' = f(x; p, q), \tag{1}$$

where $x \in \mathbb{R}^n$ are the system variables and $p, q \in \mathbb{R}$ are the parameters; we will refer to p as the control parameter and q as the auxiliary parameter. We are interested in finding regions of homeostasis in such a general model. First, we write the (implicit) equilibrium $X(p, q)$ satisfying

$$f(X(\hat{p}, \hat{q}); \hat{p}, \hat{q}) = 0. \tag{2}$$

While $X \in \mathbb{R}^n$, we are interested in homeostasis only in a single output; thus, we filter

$$Y = \Lambda(X), \quad \Lambda : \mathbb{R}^n \to \mathbb{R}. \tag{3}$$

Often this is as simple as taking a single component of X, though in our example (Sec. II B 3) it will be more complicated. $Y(p)$, in terms of the control parameter alone, is referred to as the *input-output map*. Retaining the dependence upon the auxiliary parameter q, the following properties of $Y(\hat{p}, \hat{q})$ describe the conditions for one-dimensional (1D) infinitesimal homeostasis. In particular, infinitesimal homeostasis requires only

$$\frac{\partial Y}{\partial \hat{p}} = 0, \tag{4}$$

that is, that the biological notion of having the output quantity be approximately constant with respect to the input is described (locally) by the input-output map having zero slope. This may occur in different ways. One type is *simple homeostasis* in which

$$\frac{\partial^2 Y}{\partial \hat{p}^2} \neq 0. \tag{5}$$

Another is the so-called *chair* [2,11,12], in which

$$\frac{\partial^2 Y}{\partial \hat{p}^2} = 0, \tag{6}$$

$$\frac{\partial^3 Y}{\partial \hat{p}^3} \neq 0, \quad \text{and} \tag{7}$$

$$\frac{\partial^2 Y}{\partial \hat{p} \partial \hat{q}} \neq 0. \tag{8}$$

We focus here on the chair for two reasons: (i) it is thought to be more robust and common in biological models [2,11] and (ii) its similarity to the homeostasis and transitions observed in our later example (Sec. II B 3). The chair has *universal unfolding*, which describes changes under perturbation (and up to change in coordinates) in a general form given by

$$Y(\hat{p}, \hat{q}) = \pm \hat{p}^3 + \hat{q}\hat{p} \tag{9}$$

[about the point $(\hat{p}, \hat{q}) = (0, 0)$]; this is illustrated in Fig. 2. In particular, the black curve shows the chair for $\hat{q} = 0$, while the blue and red show the unfolding perturbations for $\hat{q} = \pm\delta$ respectively. Of particular interest is the $\hat{q} = -\delta$ (red) curve which has both local minima and maxima: Thus, perturbations away from homeostatic equilibria of this type are not monotonic and can exhibit paradoxical behavior in the input-output map. That is, $\hat{q} \geqslant 0$ yields monotonic structure while $\hat{q} < 0$ gives local extrema (for the $Y = +\hat{p}^3$ form; the signs of the perturbation are swapped for $Y = -\hat{p}^3$).

While we have so far discussed the notion of infinitesimal homeostasis only in 1D (e.g., emergence via the chair unfolding), it is worth noting that similar phenomena occur in higher dimensions. For example, in two dimensions (2D), the equivalent structure (the hyperbolic umbilic) again has a universal unfolding—now with three auxiliary parameters—ranging from monotonic to four local extrema [12].

B. Lung function

In order to illustrate these concepts and demonstrate their occurrence in a biological model, we now consider an example system drawn from the study of the pathophysiology and treatment of asthma.

1. Ventilation flow configurations

Asthma is characterized by reversible airway narrowing driven by the constriction of the airway smooth muscle, as well as airway inflammation and remodeling on a longer timescale. Airway narrowing during an acute asthma exacerbation is driven by contraction of the layer of airway smooth muscle (ASM) surrounding each airway [27]. Activation of the ASM leads to force generation and muscle shortening,

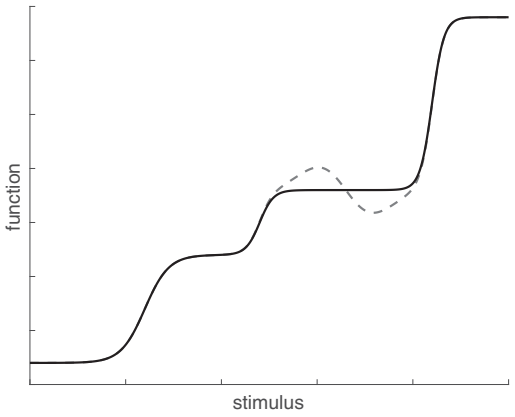

FIG. 3. Schematic illustration of transitions between flow configurations expected in the lung (black); possible unfolding with local extrema (gray, dashed).

and hence airway narrowing; the process is driven by the interaction between muscle force production dynamics and the nonlinear behavior of the airway wall [28,29]. In general, then, one might expect inhaled bronchoconstrictor stimulation of the ASM to lead to reduced ventilation throughout the lung, as ASM activation drives airway narrowing. Instead, imaging studies characteristically show ventilation patterns which exhibit both the expected areas of hypo-ventilation, but also areas of hyperventilation. This phenomenon is sometimes referred to as *clustered ventilation defects* or *ventilation heterogeneity*. Interestingly, these patterns appear to be neither entirely structural nor entirely dynamic, and as such have attracted much interest [30–33].

One important observation in modeling studies of this phenomenon is that modulation of ASM stimulus leads to transitions between (discrete) flow configurations, with recruitment and de-recruitment of portions of the lung [30,34]. As such, one might expect a stimulus response curve exhibiting these transitions and also plateaus around each configuration—this is illustrated schematically in Fig. 3. The behavior of the flow configuration beginning at zero stimulus might be expected to be homeostatic; that is, the healthy, at-rest flow configuration in the absence of ASM stimulation should be robust to modest ASM stimulus. If so, then perturbations away from this homeostatic equilibrium (in another auxilliary parameter, for example, in disease), might admit the branch of the universal unfolding which exhibits local extrema. The same process might occur for each of the flow configurations; one possible unfolding of this type is shown schematically in Fig. 3 as the gray, dashed curve. If this does occur, then it is a possible explanation for paradoxical observations in disease—the emergence of local extrema within a stimulus-function response which is expected to be monotonic means that certain responses will appear paradoxical.

2. *Paradoxical observations*

Studies of the pathophysiology of asthma abound with purported paradoxical effects. Perhaps the best known is the response to a deep inspiration (DI), wherein the patient fully inhales from functional residual capacity (FRC) all the way up to total lung capacity (TLC). DIs have been extensively studied for their ability to dilate the airways (bronchodilation). The idea is that the volumetric strain of the lung as a whole is passed on to the airways and this disrupts the contractile capacity of the ASM, at least transiently. However, it has long been known that in some patients there is a paradoxical response in which a DI appears instead to have a bronchoconstrictor (airway narrowing) effect [18,20].

Other studies demonstrating paradoxical effects include the response to positive end-expiratory pressure (PEEP) [14], paradoxical response to inhaled aerosol [17], and mixed responses in the patterns of bronchoconstriction and bronchodilation [15,16,19,21]. The response to treatment of asthma by bronchial thermoplasty (see next section) has also been shown to have a mixed response, with only a subset of patients responding to treatment [36] and also post-treatment regional flows exhibiting mixed response [37].

3. *Example: Model flow patterns in asthma and treatment bronchial thermoplasty*

As an example to illustrate the proposed concept, we consider a network flow model of lung function in asthma and predictions of response to treatment by bronchial thermoplasty (BT). BT is a relatively recent treatment for asthma in which thermal energy ($\sim 65^\circ$ C) is delivered to a relatively small number (~ 25) of relatively large (> 3 mm diameter) airways [38]. The idea is that the thermal ablation of the ASM layer reduces capacity for ASM force generation and hence airway narrowing. Because of the relatively small number of treated airways, the underlying mechanism of action has been controversial, with several proposed nonlocal mechanisms by which the treatment effect might extend from the treated central airways into the untreated peripheral airways. Recent theoretical work suggests that this mechanism is not structural but rather functional, that is, that it is airway interdependence which allows treatment of the central airways alone to propagate functionally toward the periphery by altering global flow patterns [35]. We will use this model as our example of paradoxical behavior, akin to Braess' paradox, arising from perturbed homeostasis.

A basic overview is as follows. The reader is referred to [34,35,39,40] for full details. The essential notion is of a network flow model in the asymmetric bifurcating airway tree. Each airway undergoes internal dynamics in which activation of ASM drives airway narrowing so that we write the radius for the ith airway [41] as

$$r_i' = \phi_i(\vec{r}; p, \vec{q}). \tag{10}$$

Here we think of the control parameter p as ASM activation, along with structural parameters $\vec{q}$ which describe all aspects of the airway tree structure (airway lengths, airway wall, and ASM thickness, etc.). Adding flow conservation at junctions, pressure balance, and quasisteady Poiseuille flow in each segment yields a system of differential algebraic equations (DAEs). The breathing control model assumes that driving pressures (e.g., generated by the diaphragm) increase to maintain target flow and volume [40]. However, it is possible to systematically eliminate the algebraic constraints to obtain a system of first-order ODEs only [39]. Hence the system can

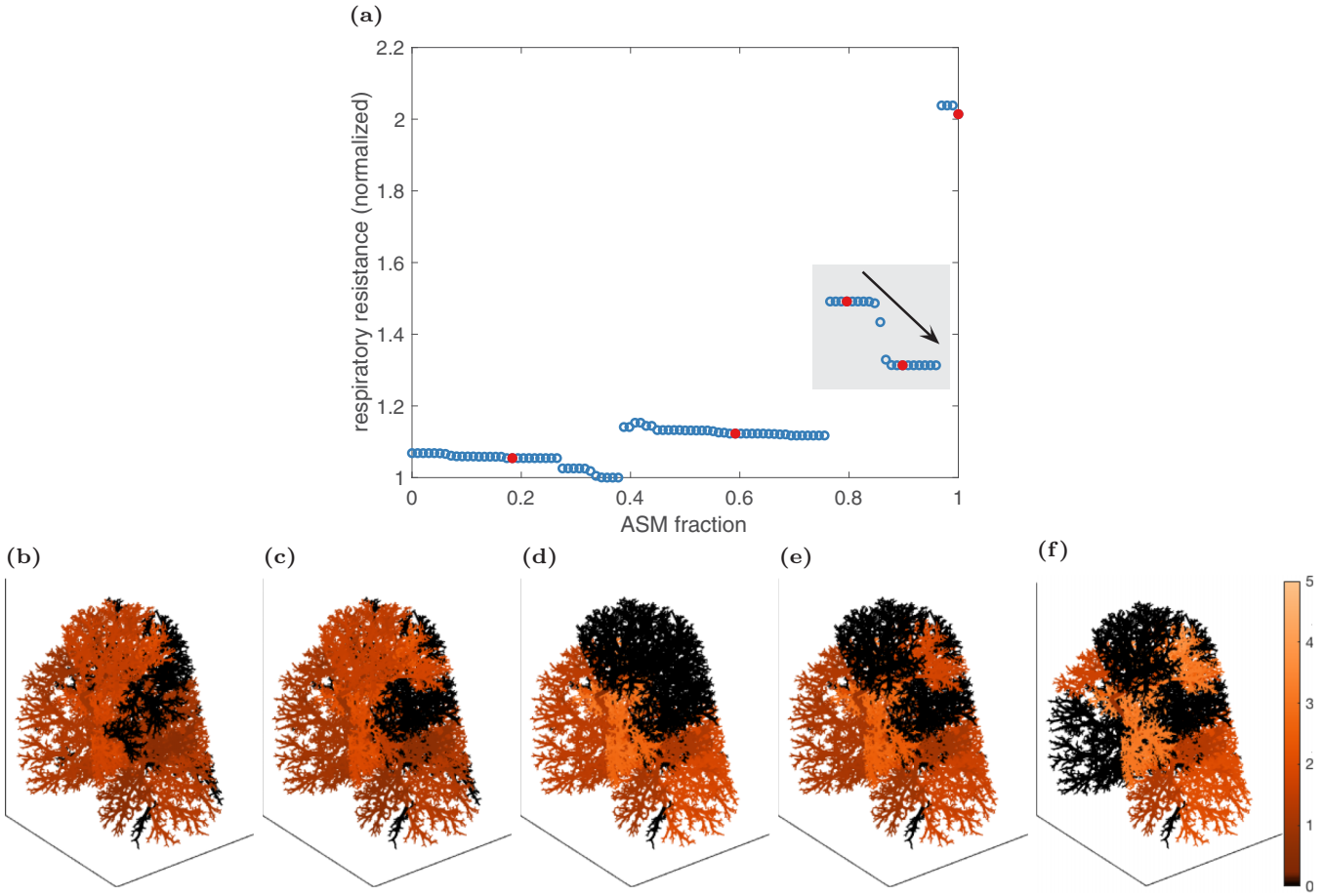

FIG. 4. Input-output map for a fatal asthma simulated lung; input is the ASM fraction remaining after treatment (in the treated airways), while output is the respiratory resistance (at 85% of maximal ASM activation). Region of paradoxical response is highlighted (a). Panels (b) through (f) show flow configurations at selected points (red circles in panel (a), ordered left to right). The color bar indicates flow normalized to nominal [35]. Note in particular that panels (d) and (e) straddle the paradoxical response, with panel (e) exhibiting recruitment in the upper lobe and a visually more homogeneous flow pattern.

be written as

$$\vec{r}\,' = \Phi(\vec{r}; p, \vec{q}), \tag{11}$$

that is, exactly in the form of Eq. (1). Here we are thinking of the control parameter p representing total ASM activity (both activation and potential ablation in treatment) and the structural parameters of all the airways in the parameter vector $\vec{q}$. These structural parameters are determined by a statistical model calibrated from extensive human lung specimens [35]. The dimensionality of the system is large; for a single human lung there are approximately 30 000 airways.

Averaging out the breathing oscillations, the equilibrium solutions $\rho(p, \vec{q})$ then satisfy

$$0 = \Phi(\rho(p, \vec{q}); p, \vec{q}) \tag{12}$$

and we filter by calculating the respiratory resistance $R(\rho(p, \vec{q}))$ (for the whole lung [42,43]), and hence our input-output map describes respiratory resistance as a function of the ASM fraction. Figure 4 shows a simulation of this input-output map for a lung with structural parameters ($\vec{q}$) calibrated for fatal asthma [44], along with illustrations of the discrete flow configurations at selected locations (red circles).

Because asthma involves extensive airway remodeling, the structural parameters $\vec{q}$ are altered in disease. Such changes can be viewed as perturbing the homeostatic equilbria which would be expected to exist in the absence of disease. Indeed, such a perturbation might lead to the branch of the universal unfolding which generates local extrema, and thus we would expect to see paradoxical behavior in some circumstances. Indeed, the simulation shown in Fig. 4 demonstrates this clearly; while increasing ASM fraction would be expected (naively) to increase respiratory resistance monotonically, instead there are regions of paradoxical response (negative slope) within an overall response with positive slope.

Within a network flow context, this can be viewed as a form of Braess' paradox; that is, the alteration to the network (ablation of ASM) which was intended to improve flow through the network has instead had the reverse effect and instead impeded flow. This is also consistent with clinical studies which indicate a mixed response to BT [36].

It is also useful to compare the input-output maps for a range of simulations, rather than a single example, and also compare with a nonasthma population. Of course, BT would

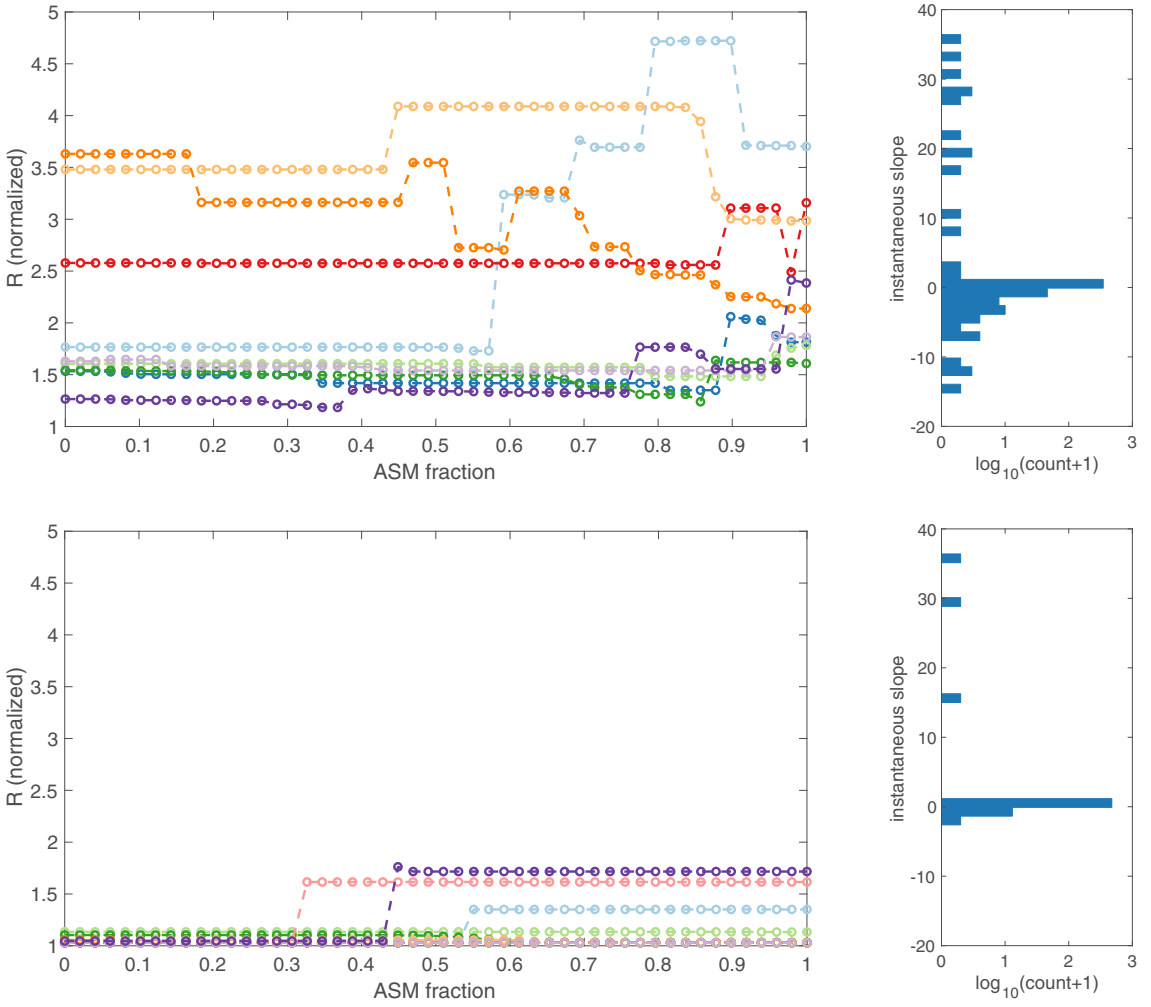

FIG. 5. Input-output maps (left); comparison between fatal asthma (upper panels) and nonasthma (lower panels). As in Fig. 4, input is the ASM fraction remaining after treatment (in the treated airways), while output is the respiratory resistance (at 85% of maximal ASM activation). Histograms of the instantaneous slope are shown in the right-hand panels (log scale). Fatal asthma maps (upper panels) exhibit nonmonotonic, paradoxical behavior, with significant occurrence of negative slope. Nonasthma maps (lower panels) are predominantly homeostatic and/or monotonic, with slope exclusively near zero or positive. Ten simulations are shown for each group.

not be used on a nonasthma population, but our expectation is that the resulting input-output maps (for respiratory resistance as a function of ASM fraction) should, for this population, be closer to homeostatic. That is, that the equivalent nonasthma simulations will not exhibit paradoxical behavior arising from the perturbation of homeostasis. The cohort simulation input-output maps are shown in Fig. 5, with input-output maps for fatal asthma simulations in the upper left and for nonasthma simulations in the lower left. Indeed, the fatal asthma cohort exhibits much greater paradoxical behavior than the nonasthma cohort, which is largely homeostatic and monotonic. This is quantified explicitly in the righthand panels in terms of the instantaneous slopes calculated from each map; intuitively we expect increasing ASM fraction to increase R, and hence positive slope is expected. Indeed, the nonasthma cohort does show almost exclusively zero and positive slope, while the fatal asthma group has significant occurrence of negative slope, corresponding to regions of paradoxical behavior.

III. DISCUSSION

In this paper, we have proposed the notion that homeostasis in biological systems might give rise to paradoxical behavior in perturbed equilibrium situations, such as disease, via the universal unfolding of infinitesimal homeostasis. We have illustrated this idea both conceptually and using a specific example drawn from studies of the pathophysiology of the lung in asthma. Indeed the paradoxical response of the asthmatic lung to treatment can be viewed both in this context and also as a form of Braess' paradox when the problem is viewed as one of network flow. That is, the structural alterations to the flow network—in this case, ASM ablation, which is intended to improve overall function—instead can have a detrimental effect. That this behavior emerges from a perturbation away from homeostasis is supported by the observation that this paradoxical behavior is much more common in disease than in nonasthma simulations.

It is worth noting that while we have used the post-BT residual fraction of ASM in the treated airways as our control parameter, it is also almost certainly possible to demonstrate the same effect in a non-BT lung model. One obvious possibility would be using the degree of overall ASM activation as the control parameter; the same (perturbed) homeostatic transitions are at work. Equally, bronchodilator response might demonstrate the (reverse) paradoxical effect, as well as other system modifications such as DI response and more. Indeed, it is plausible that many of the paradoxical observations noted in Sec. II B 2 might emerge via similar mechanisms. Although such hypotheses would be relatively easy to test experimentally, most published data does not allow for such a comparison, principally for two reasons: (i) Dose response is generally given as a cohort average, rather than individual responses, which masks regions of paradoxical response, and (ii) dose graduations are generally not fine enough to display detailed structure. Those few studies which do allow comparison offer some support to the general hypothesis, for example, pulmonary resistance as a function of methacholine dose [45,46] and forced expiratory volume in one second (FEV1) as a function of histamine or benzalkonium chloride dose [47].

This theoretical framework might also be used to improve the treatment of asthma, both in a BT-specific context and more generally. For BT, the idea would be to design tailored treatments which are optimal for each patient and avoid the regions of paradoxical response. Similarly, other changes such PEEP, DIs, bronchodilators, and more, which have been thought to exhibit paradoxical response, could also potentially benefit from more subtle targeting which takes account of any nonmonotonic response.

We also have only shown indirectly that the presumably homeostatic cohort (nonasthma) exhibits near monotonic behavior, while the presumably perturbed cohort (fatal asthma) has significant regions of paradoxical behavior. In principle, it would be possible to directly identify the points of infinitesimal homeostasis and their unfoldings [2,11] in order to understand this relationship explicitly. However, such methods are tractable only in simpler situations, either models of a specific form for analytic understanding or of smaller dimensionality for numerical approaches. Efficiently locating points of infinitesimal homeostasis in a general models remains an open problem. To see why this is challenging, consider that in Figs. 4 and 5 we have found regions of (presumed) homeostasis in which we might search nearby for a specific form of infinitesimal homeostasis (e.g., a chair). However, consider the search space: Even assuming we know the control parameter, for a model with n parameters (e.g., $\vec{q} \in \mathbb{R}^n$), we must search within this n-dimensional space for a singularity of low codimension. In essence, we do not know which parameter (of combination thereof) is the auxilliary parameter or for which values of the remaining parameters the point of infinitesimal homeostasis exists.

It is also interesting to consider the traffic network analogy further with respect to the probability of observing paradoxical behavior in congested network flows. For example, it has been shown, under certain (reasonably general) conditions that traffic network perturbations are about as likely as not to exhibit Braess' paradox [48]. Indeed, the perturbed infinitesimal homeostasis mechanism suggests a similar conclusion, with arbitrary perturbations of the auxiliary parameter just as likely to fall onto the local extrema branch as the monotonic branch.

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