

# Mathematical modelling of cell adhesion in asthma

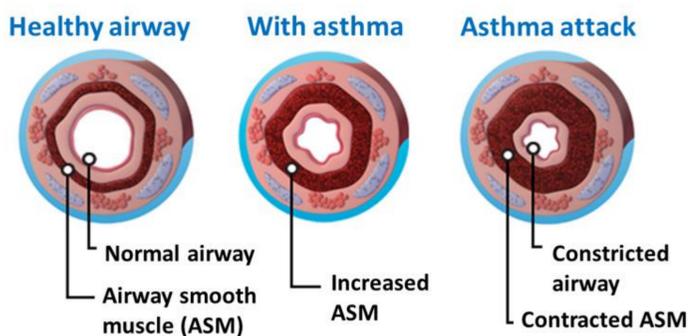
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## 1. Asthma affects over 1 in 12 people in the UK

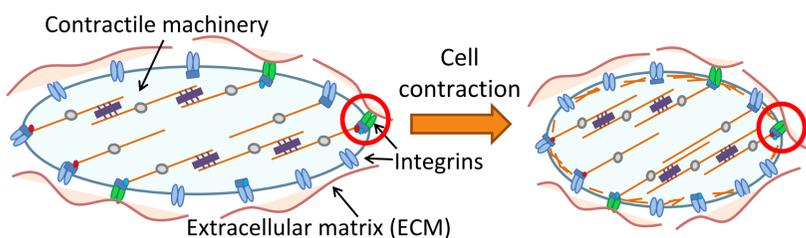
- Asthma is a lung disease for which there is currently no cure. The disease greatly affects quality of life.
- In the UK, asthma attacks lead to a hospital admission every 8 minutes and cause over 1000 deaths annually.
- This costs the NHS over £1.1 billion per year, with further economic impact due to absences from work.



**Figure 1:** During an asthma attack, the airways narrow. This restricts airflow and makes breathing difficult. (Image from houstonlungclinic.com/bronchial-thermoplasty)

## 2. Integrins regulate airway narrowing

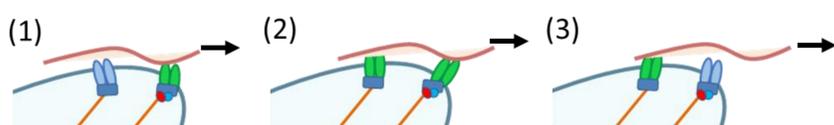
- During an asthma attack, contraction of airway smooth muscle (ASM) cells leads to airway narrowing.
- Bound integrins (green) transmit contractile force from the cells to the surrounding ‘extracellular matrix’ (ECM).



**Figure 2:** ASM cells contract during an asthma attack which causes airway narrowing. Cells adhere to the ECM via integrins, and the number of bound integrins (green) regulates the extent of narrowing.

## 3. We use mathematical models to study integrins

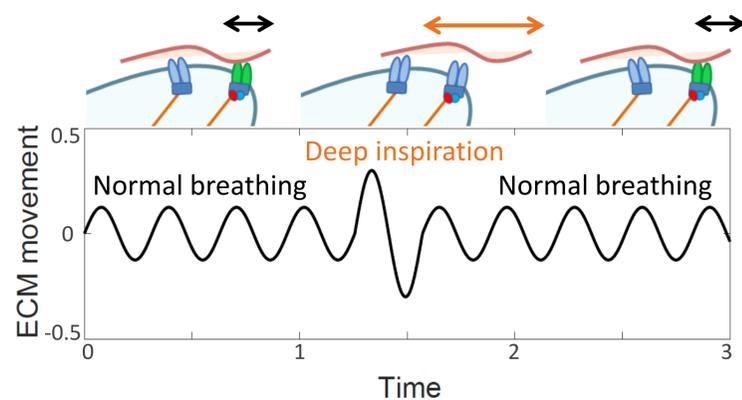
- We have made mathematical models to study how integrins respond to mechanical strains from breathing.
- Using computer simulations, we track changes in bound integrins (which may unbind) over time. This level of detail cannot currently be measured by experiments.



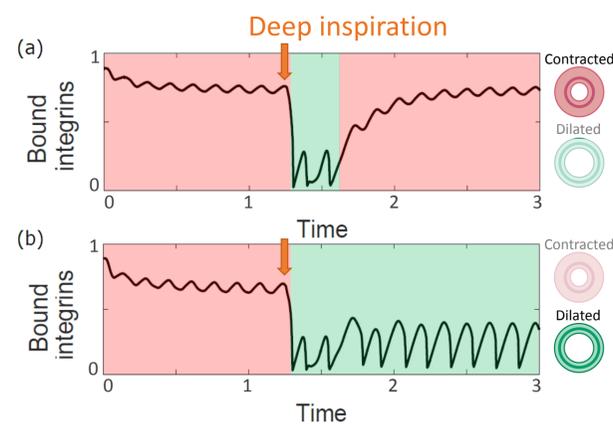
**Figure 3:** Bound integrins (green) can unbind (blue) during ECM movement. We model binding and unbinding of integrins during breathing, since bound integrins will regulate airway narrowing.

## 4. Investigation: Deep breaths to reverse airway narrowing

- Deep inspirations can reverse airway narrowing in healthy individuals, but not in asthmatics (refs [1-3]). This is not yet understood, but may be key to future therapy.
- Using our model, we investigate how a deep inspiration taken during normal breathing (Fig. 4) could affect the bound integrins (Fig. 5).



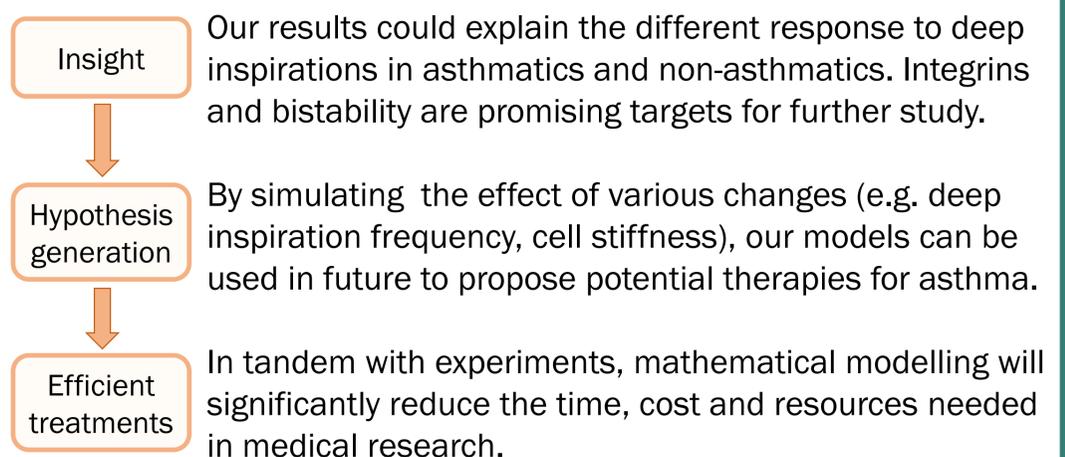
**Figure 4:** We simulate back-and-forth movement of the ECM to represent normal breathing and a larger deep inspiration.



**Figure 5:** Two possible outcomes occur after the simulated deep inspiration (DI). In (a) integrins return to a highly bound state. In (b) the DI leads to a permanently low-bound state. Since bound integrins regulate airway narrowing, we hypothesise that the high (red) and low (green) integrin states correspond to contracted and dilated airways, as observed to occur after DIs in experiments.

- The existence of two outcomes is due to a phenomenon known as bistability, which we are able to explore in the model (ref [4]).
- One of the factors that determines which outcome occurs is the amplitude of normal breathing. Breathing is typically shallower in asthmatics due to stiffer airways.

## 5. Our models provide insight and targets for future research



## References

1. Kapsali et al. (2000). Potent bronchoprotective effect of deep inspiration and its absence in asthma. *J. Appl. Physiol.* 89:711–720.
2. Crimi et al. (2002). Deep breaths, methacholine, and airway narrowing in healthy and mild asthmatic subjects. *J. Appl. Physiol.* 93:1384–1390.
3. Scichilone et al. (2000). Deep inspiration-induced bronchoprotection is stronger than bronchodilation. *Am. J. Respir. Crit. Care Med.* 162:910–916.
4. Irons et al. (Submitted to *Biophys J*, 2017) Effect of loading history on airway smooth muscle cell-matrix adhesions.

