Parametric sequence alignment

Based on Chapter 13 from *Algorithms on Strings, Trees, and Sequences* by Dan Gusfield

(pairwise) sequence alignment

Given

- a pair of sequences $S=\{s_1,s_2\}$ with lengths m and n, and
- an alignment objective function

find an 2 x L matrix

- where $\max(m,n) < L < m+n$,
- each row represents one sequence from the set with inserted gaps, and
- is optimal under the objective function.

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O(mn) running time

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When we look at it as a whole, we are defining the whole alignment score $f(\mathbb{A})$:

- with Needleman-Wunch it was

$$f_{\vec{\sigma}}(\mathbb{A}) = \sum_{a,b \in \Sigma \cup \{'-'\}} \sigma(a,b) \times \#(\mathbb{A}, a, b)$$

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- this is many times "simplified" (here simplified means fewer parameters) to

$$f_{\alpha,\beta,\gamma}(\mathbb{A}) = \alpha \sum_{a \in \Sigma} \#(\mathbb{A}, a, a) + \beta \sum_{a \neq b \in \Sigma} \#(\mathbb{A}, a, b) + \gamma \left(\sum_{a \in \Sigma} \#(\mathbb{A}, a, '-') + \sum_{b \in \Sigma} \#(\mathbb{A}, '-', b) \right)$$

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- we typically actually simplify this to

$$f_{\alpha,\beta,\gamma}(\mathbb{A}) = \alpha \cdot \text{mt}_{\mathbb{A}} + \beta \cdot \text{ms}_{\mathbb{A}} + \gamma \cdot \text{id}_{\mathbb{A}}$$

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- what about when we add affine gaps?

Alignment objective function

$$f_{\alpha,\beta,\gamma,\delta}(\mathbb{A}) = \alpha \cdot \mathbf{mt}_{\mathbb{A}} - \beta \cdot \mathbf{ms}_{\mathbb{A}} - \gamma \cdot \mathbf{id}_{\mathbb{A}} - \delta \cdot \mathbf{gp}_{\mathbb{A}}$$

- $\text{mt}_{\mathbb{A}}$ -- number of columns where both characters match
- $\text{ms}_{\mathbb{A}}$ -- number of columns where there characters are different (mismatches)
- $\text{id}_{\mathbb{A}}$ -- number of gap characters (indels)
- $\text{gp}_{\mathbb{A}}$ -- number of gaps

An example

s_1 = AACCCG
s_1 = AAGGCC

$\mathbb{A}_1$

```
AA--CCCG
AAGGCC--
```

	$\mathbb{A}_1$
mt	4
ms	0
id	4
gp	2

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s_1 = AACCCG
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$\mathbb{A}_3$
```
AACCCG
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```

$\mathbb{A}_4$
```
AAC-CCG
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```

	$\mathbb{A}_1$	$\mathbb{A}_2$	$\mathbb{A}_3$	$\mathbb{A}_4$
mt	4	4	3	4
ms	0	1	3	1
id	4	2	0	2
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Question: what values of α,β,ɣ, and δ should we choose to get the “best” alignment?

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What do we even mean by "best"?

A Digression on Accuracy

How would we know how accurate an alignment was if we knew the right answer?

The **sum-of-pairs** accuracy measures the fraction of substitutions from the ground truth alignment that are recovered in a computed alignment

Ground Truth	Computed Alignments	
`A A C C C G`	`A A C – C C G`	`A A – C C C G`
`A A G G C C`	`A A G G C C –`	`A A G G C C –`

Ground Truth **Computed Alignments**

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50%

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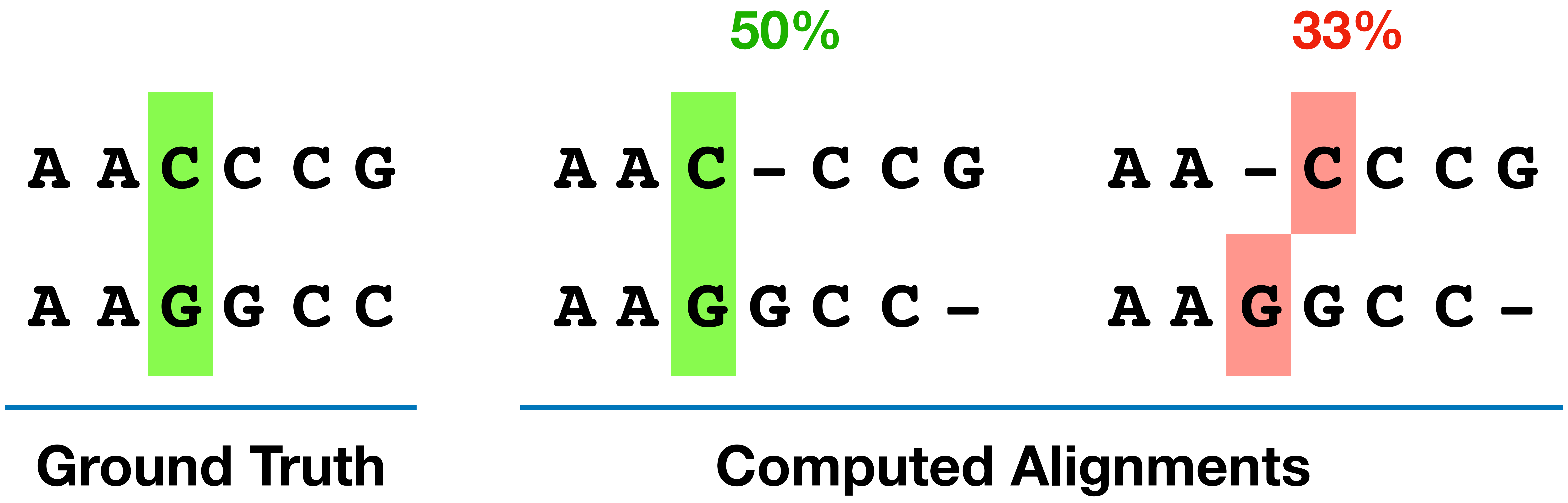

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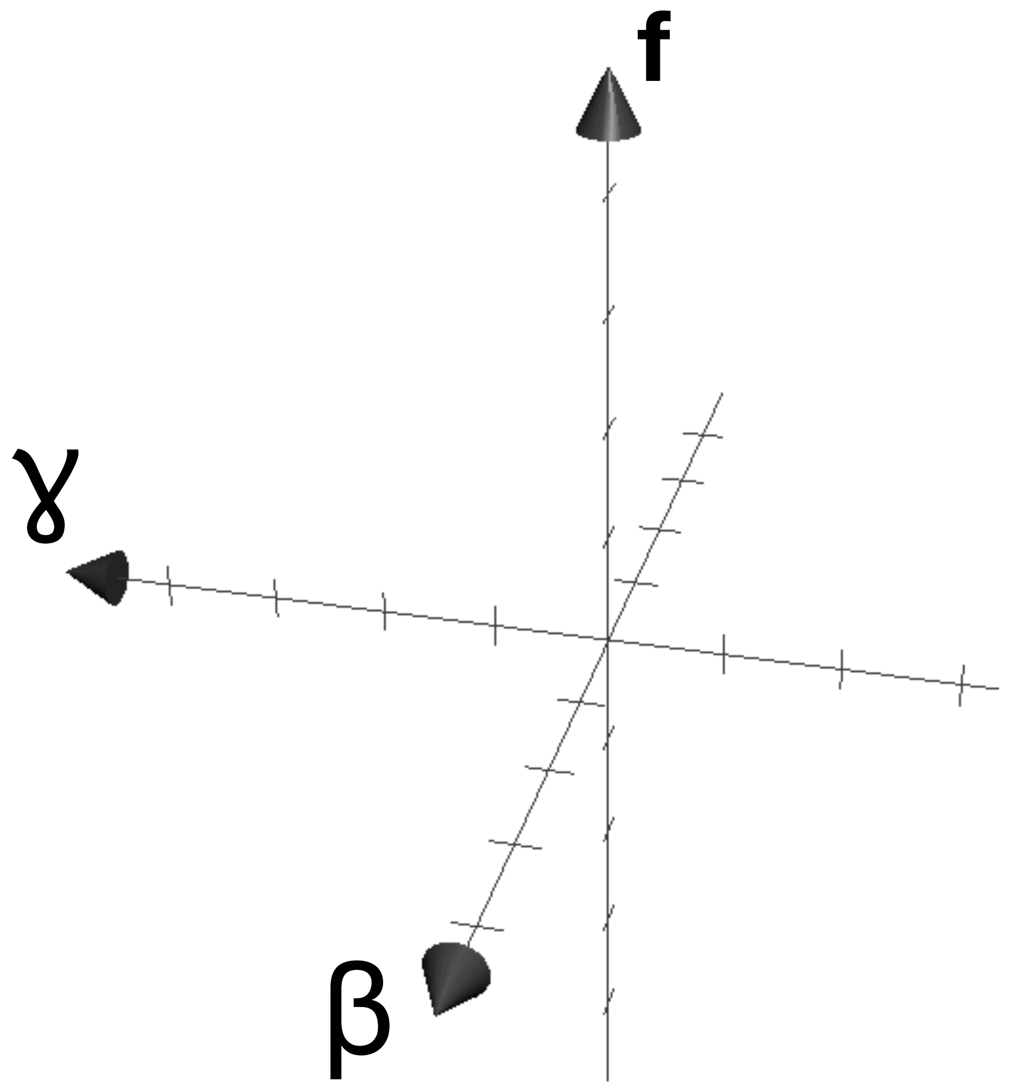
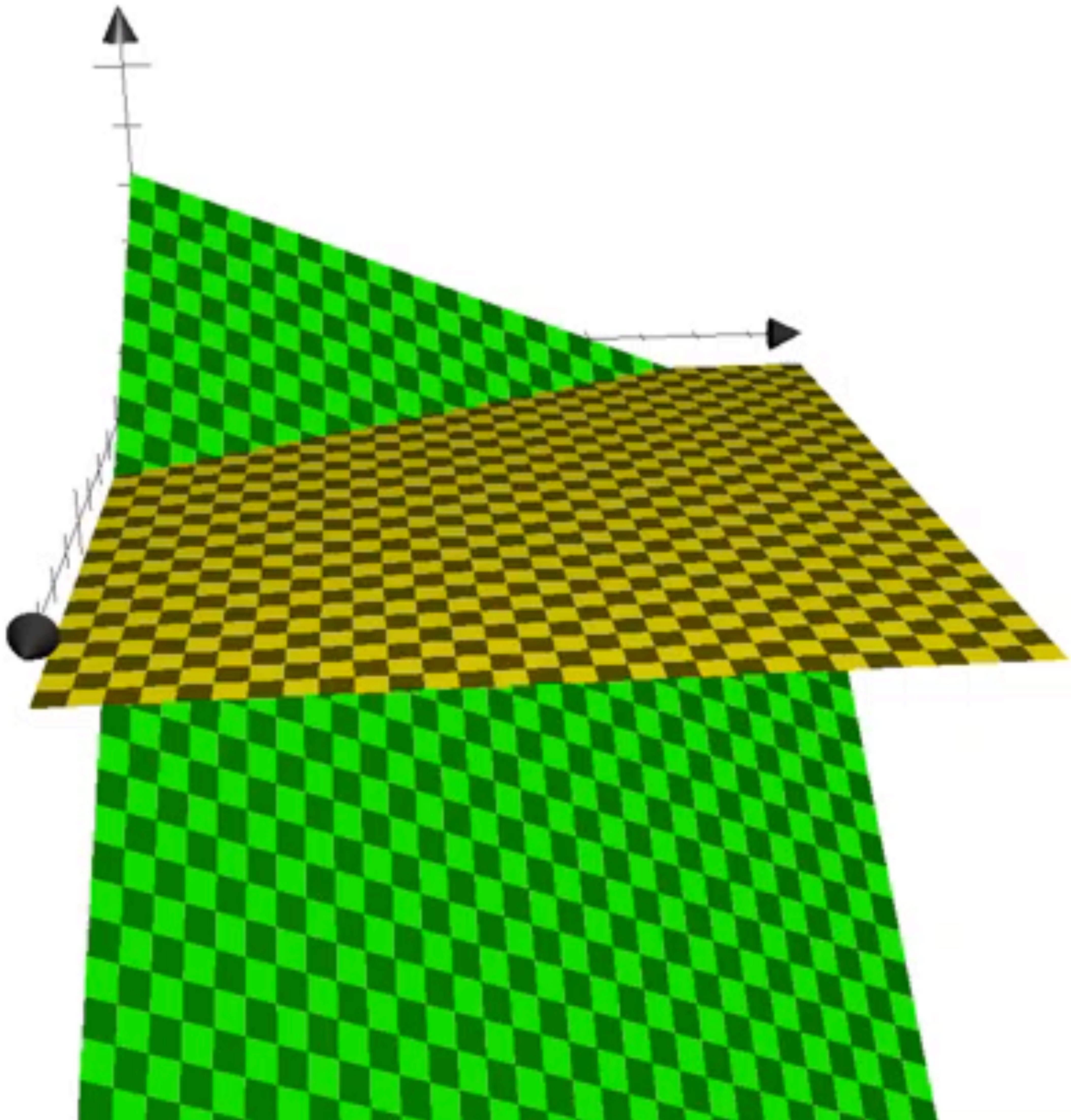
Question: what values of ~~α,β,~~ γ, and δ should we choose to get the “best” alignment?

Pairs of alignments in parameter space

Each alignment can be represented as a plane in the (ɣ, δ, f)-space.

If the planes of alignments 𝔸 & 𝔸' intersect, and are distinct, then there is a line L in (ɣ, δ, f)-space along which 𝔸 & 𝔸' have the same objective value. If the planes don't intersect then one alignment had a larger objective value at all assignments of ɣ & δ.





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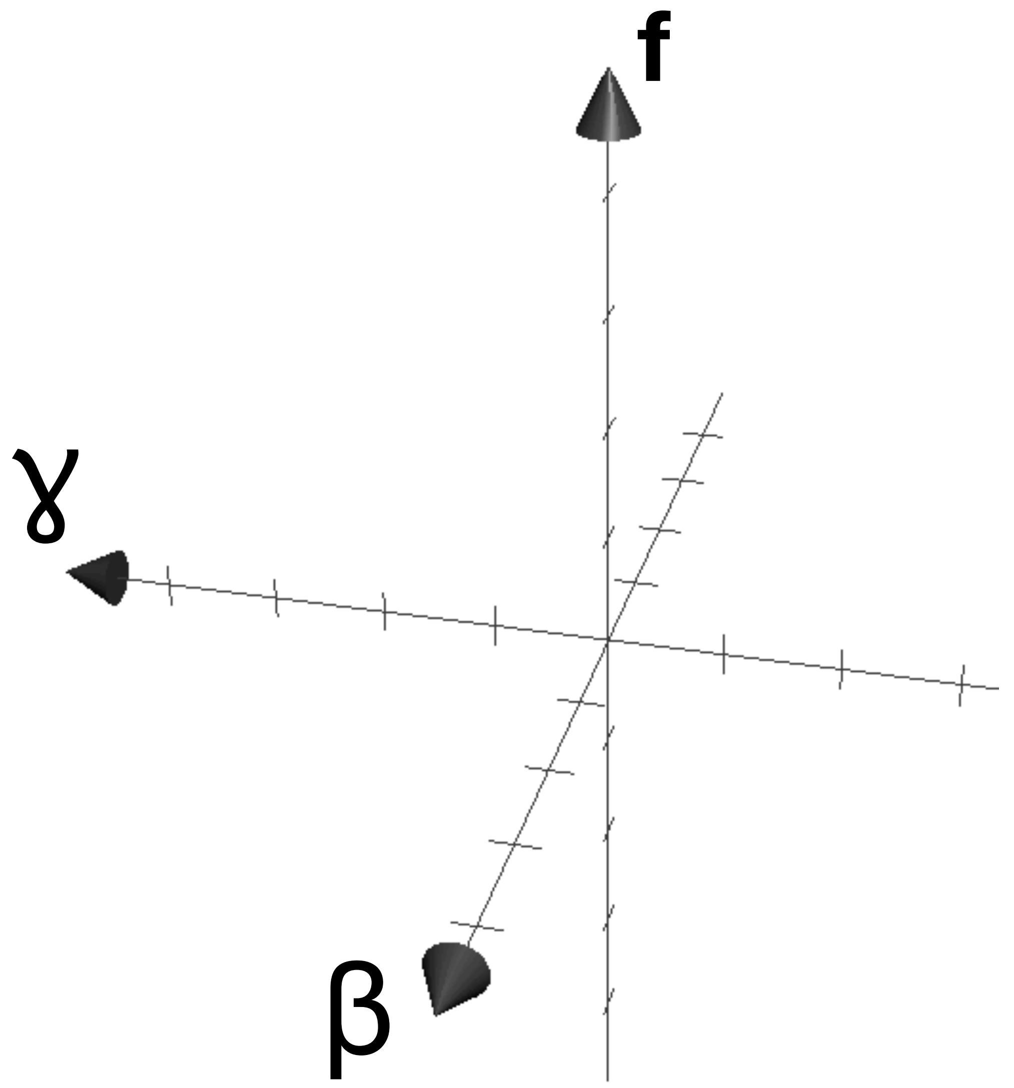

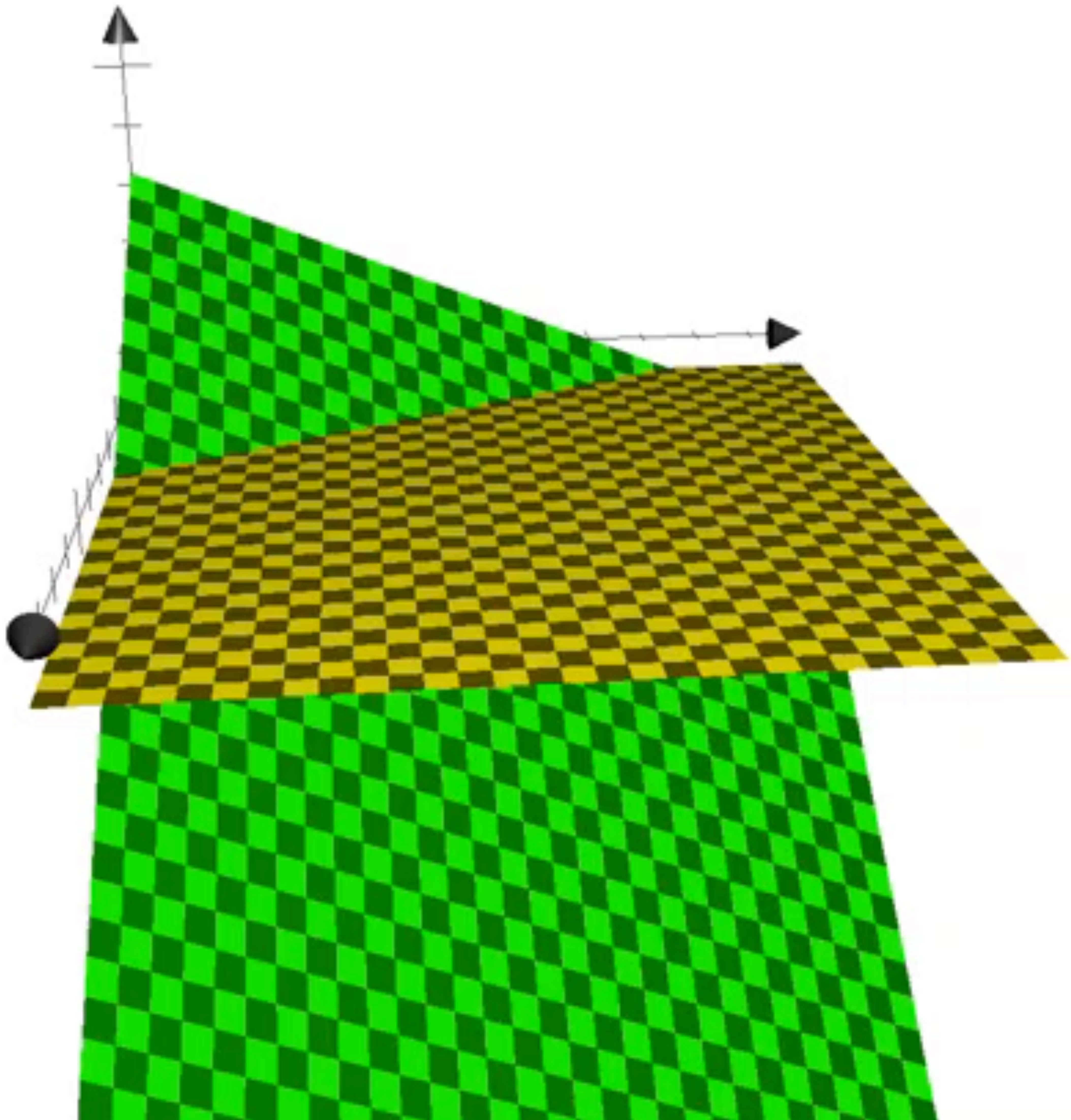

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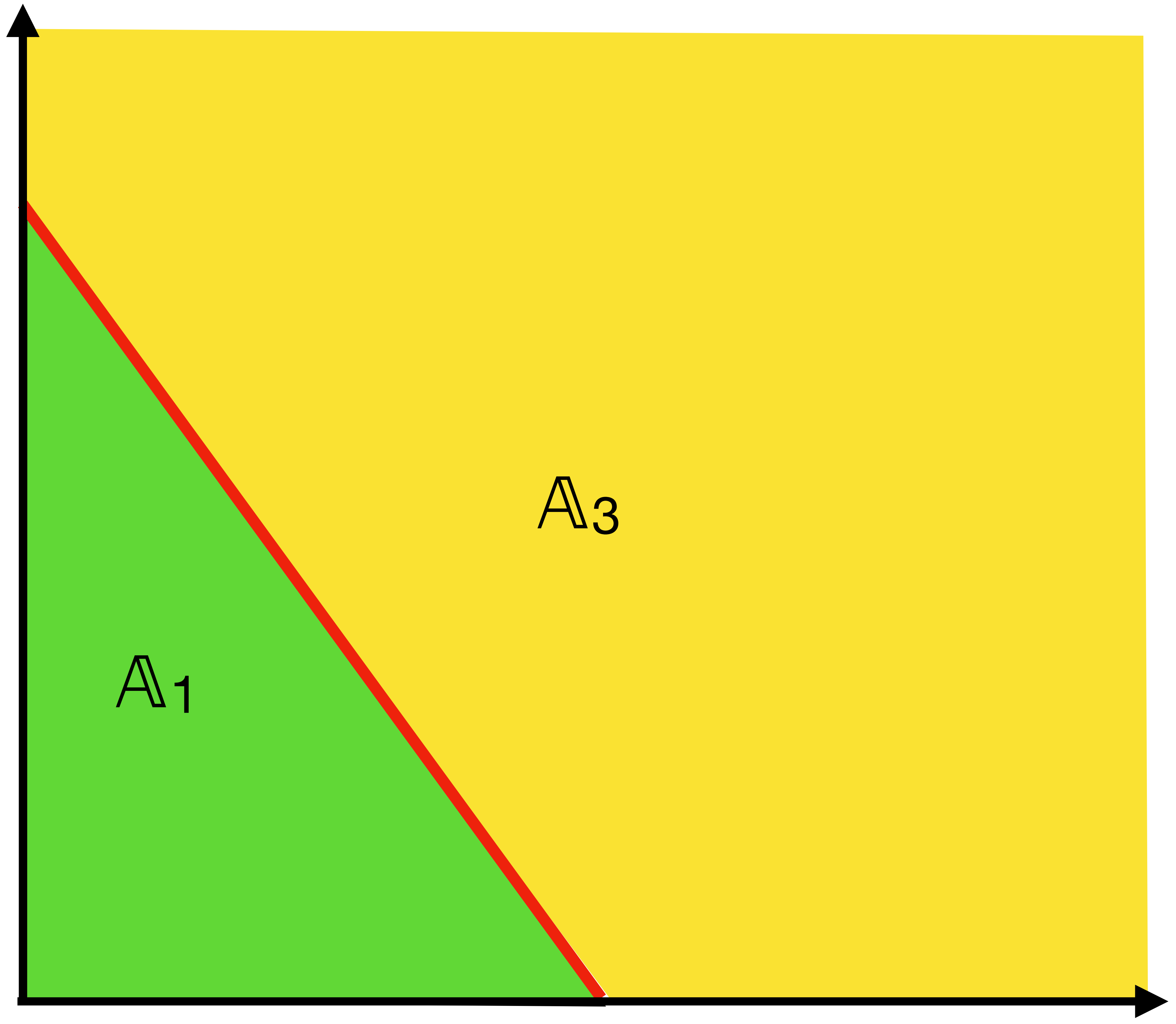
If the planes of alignments 𝔸 & 𝔸' intersect, and are distinct, then there is a line L in **(ɣ, δ)-space** along which 𝔸 & 𝔸' have the same objective value; 𝔸 has a larger value on one half plane and 𝔸' on he other. If the planes don't intersect then one alignment had a larger objective value at all assignments of ɣ & δ.

When projected to the (ɣ, δ)-plane, we can designate regions for which f(𝔸)>f(𝔸') and vice versa



Things we know so far

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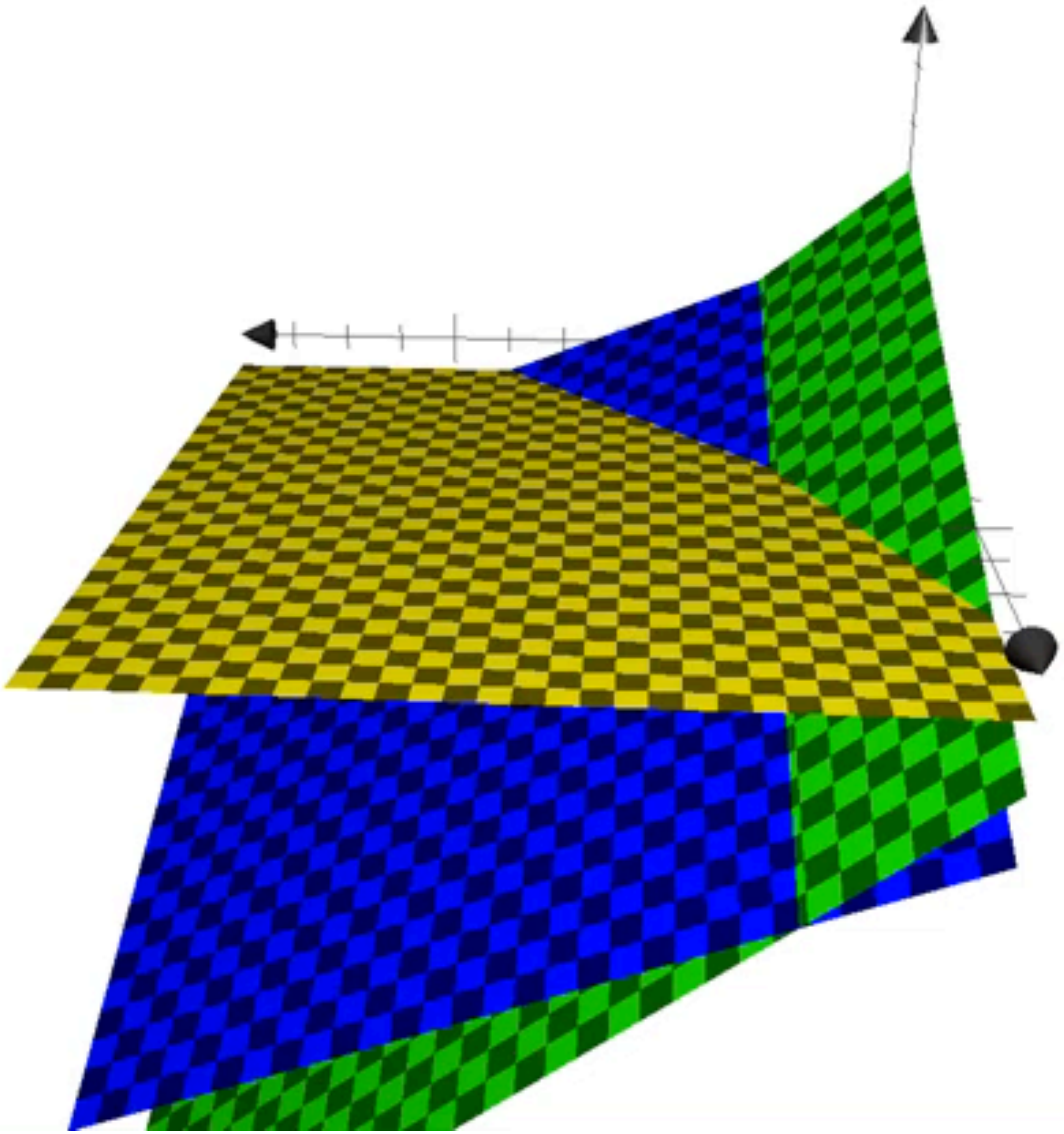
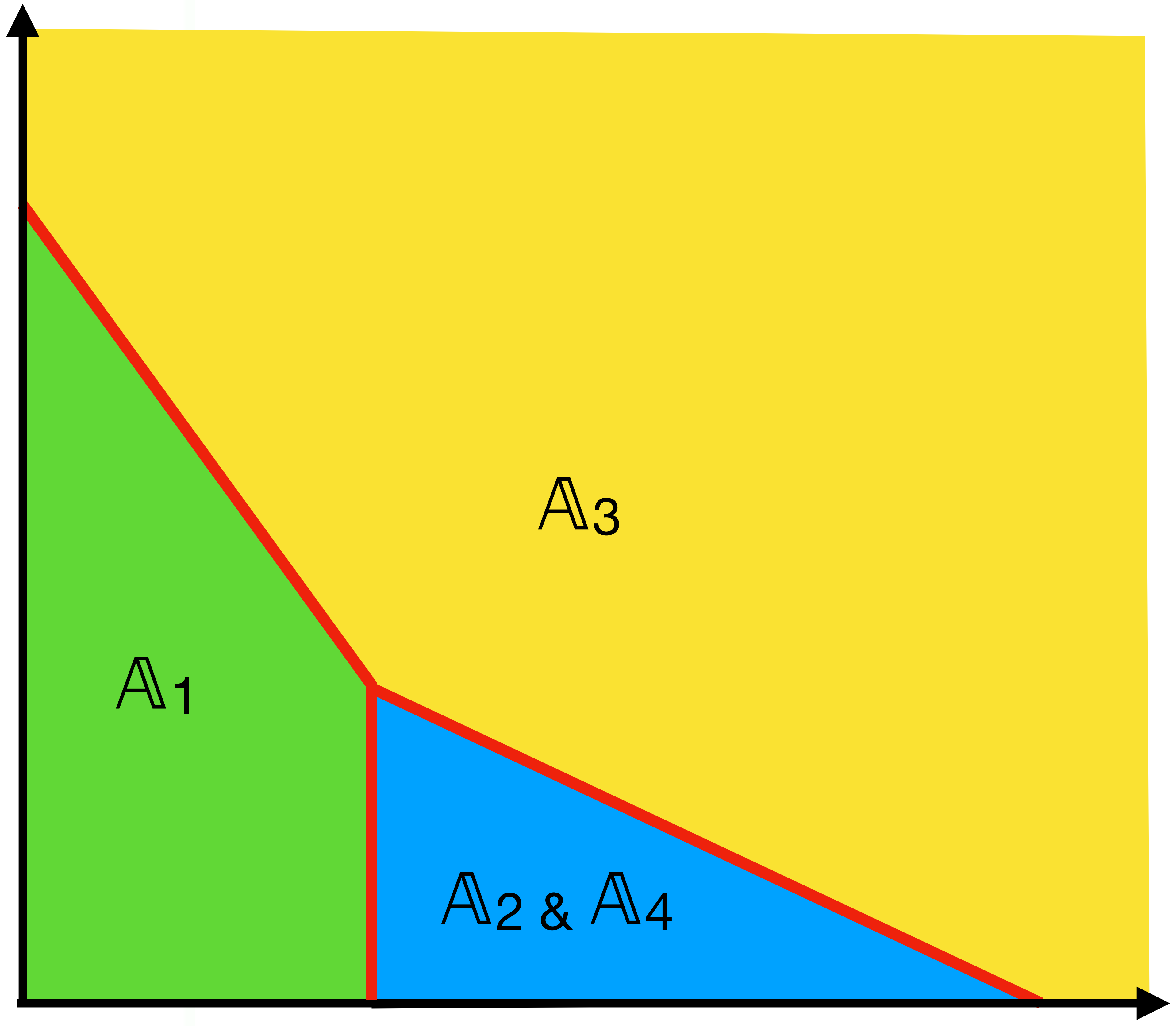
Alignments in parameter space





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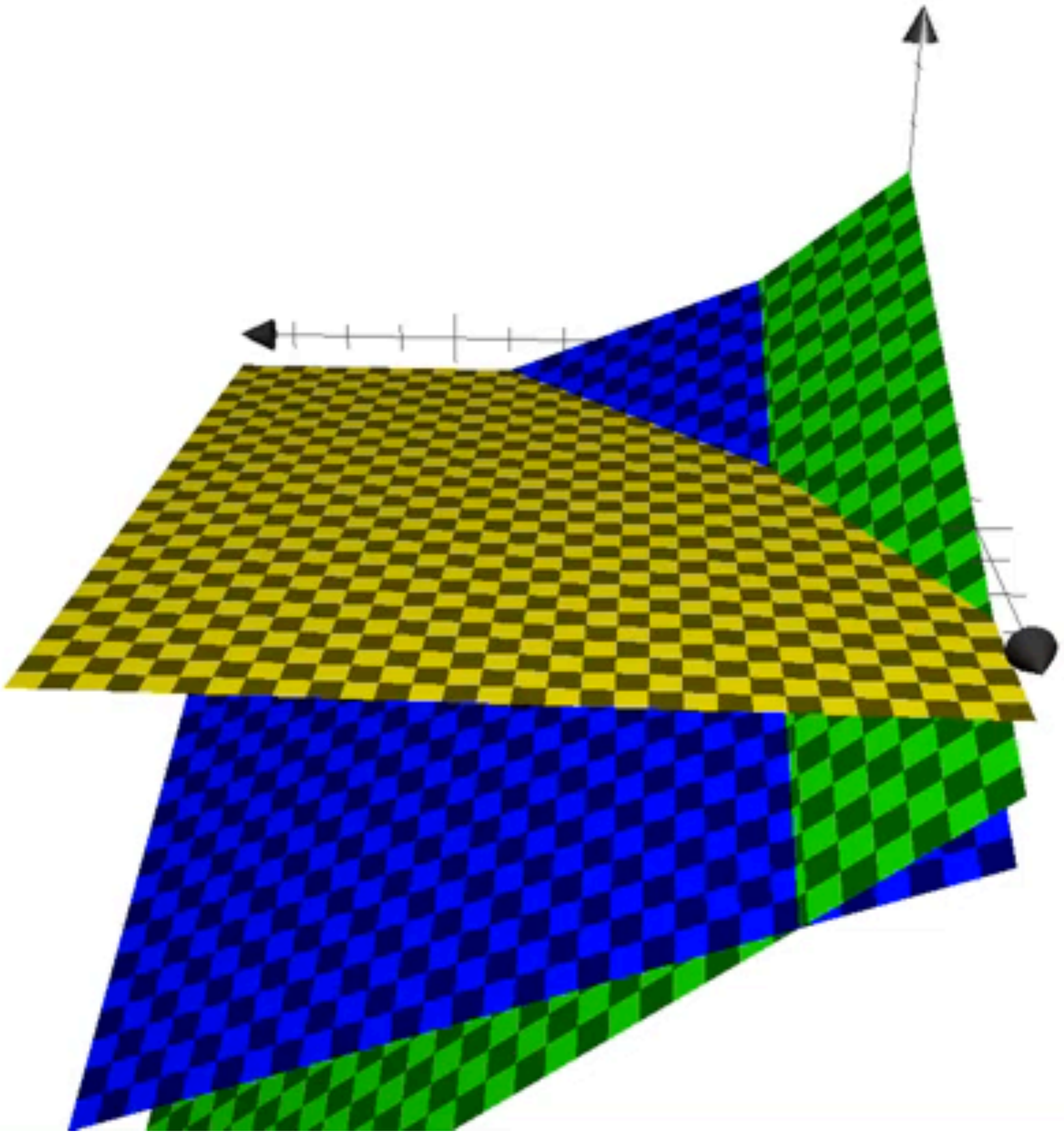
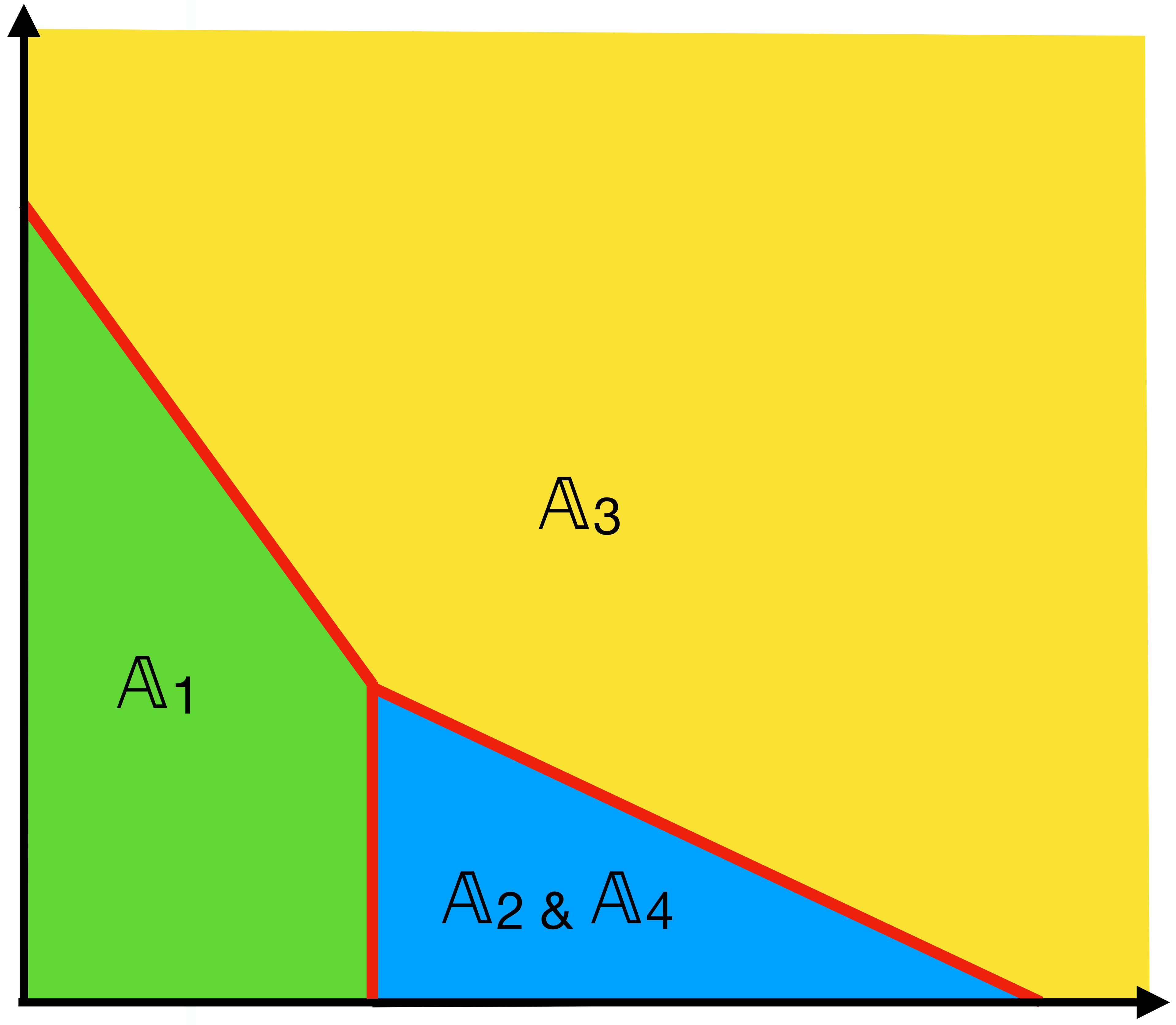
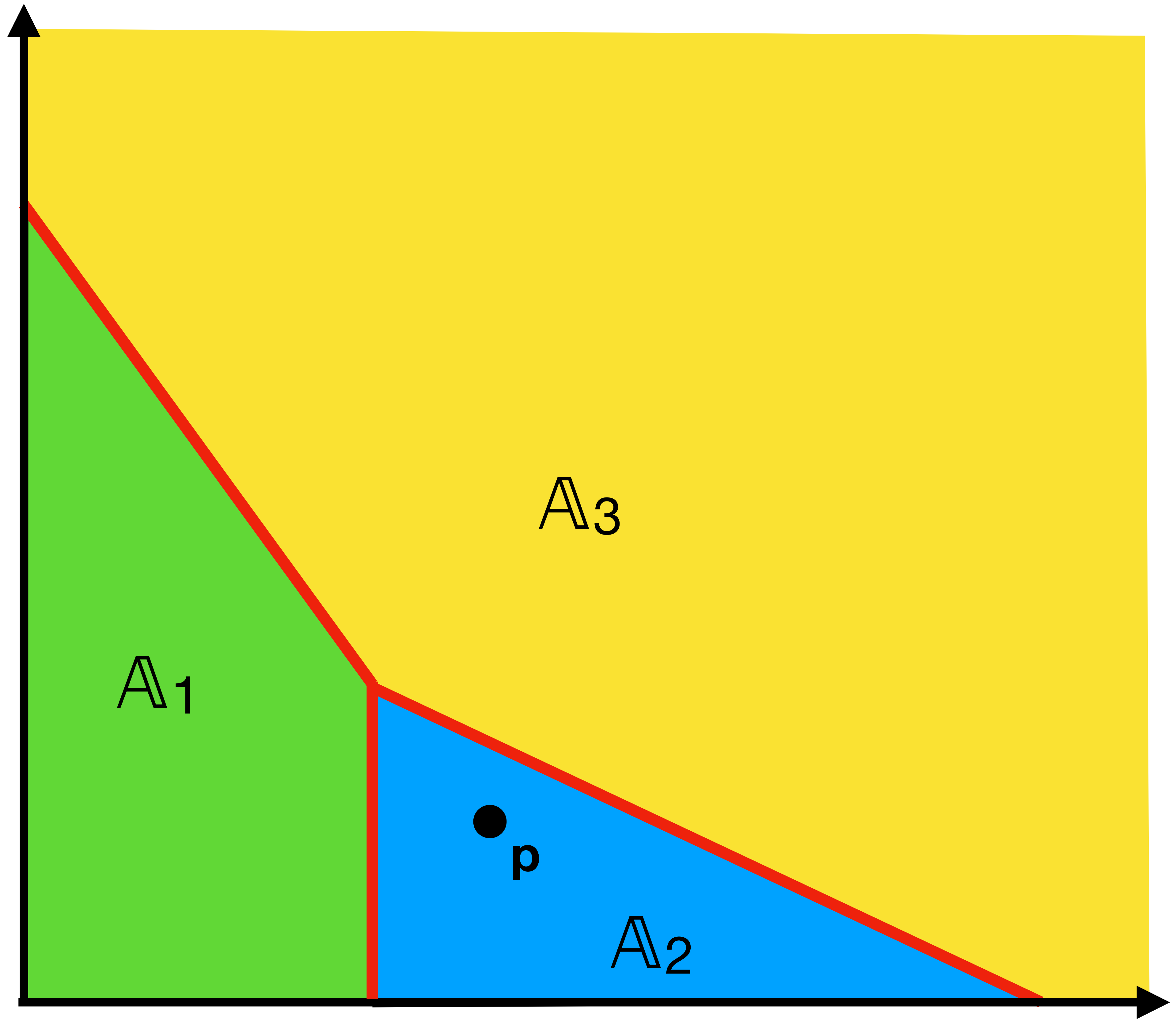




Alignments in parameter space

If $\mathbb{A}$ is optimal at some point p, it is on the correct side of the line that separates $\mathbb{A}$ from all $\mathbb{A}'$.



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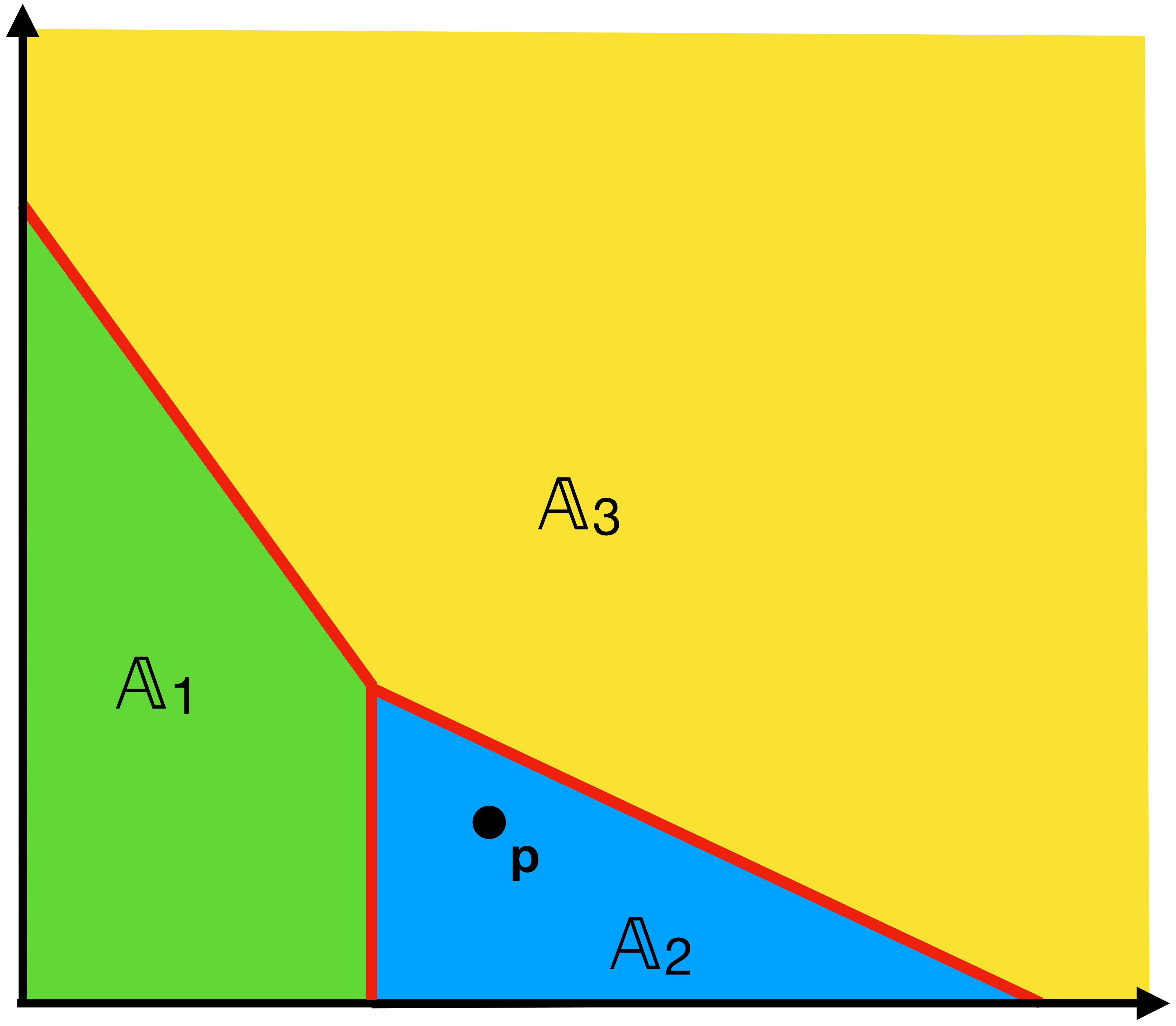
If $\mathbb{A}$ is optimal for at least 1 point p in the (ɣ, δ)-space then it is optimal for:

(1) only point p,
(2) only a line segment that contains p, or
(3) a convex polygon that contains p



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If $\mathbb{A}$ is optimal for at least 1 point p in the (γ, δ)-space then it is optimal for:

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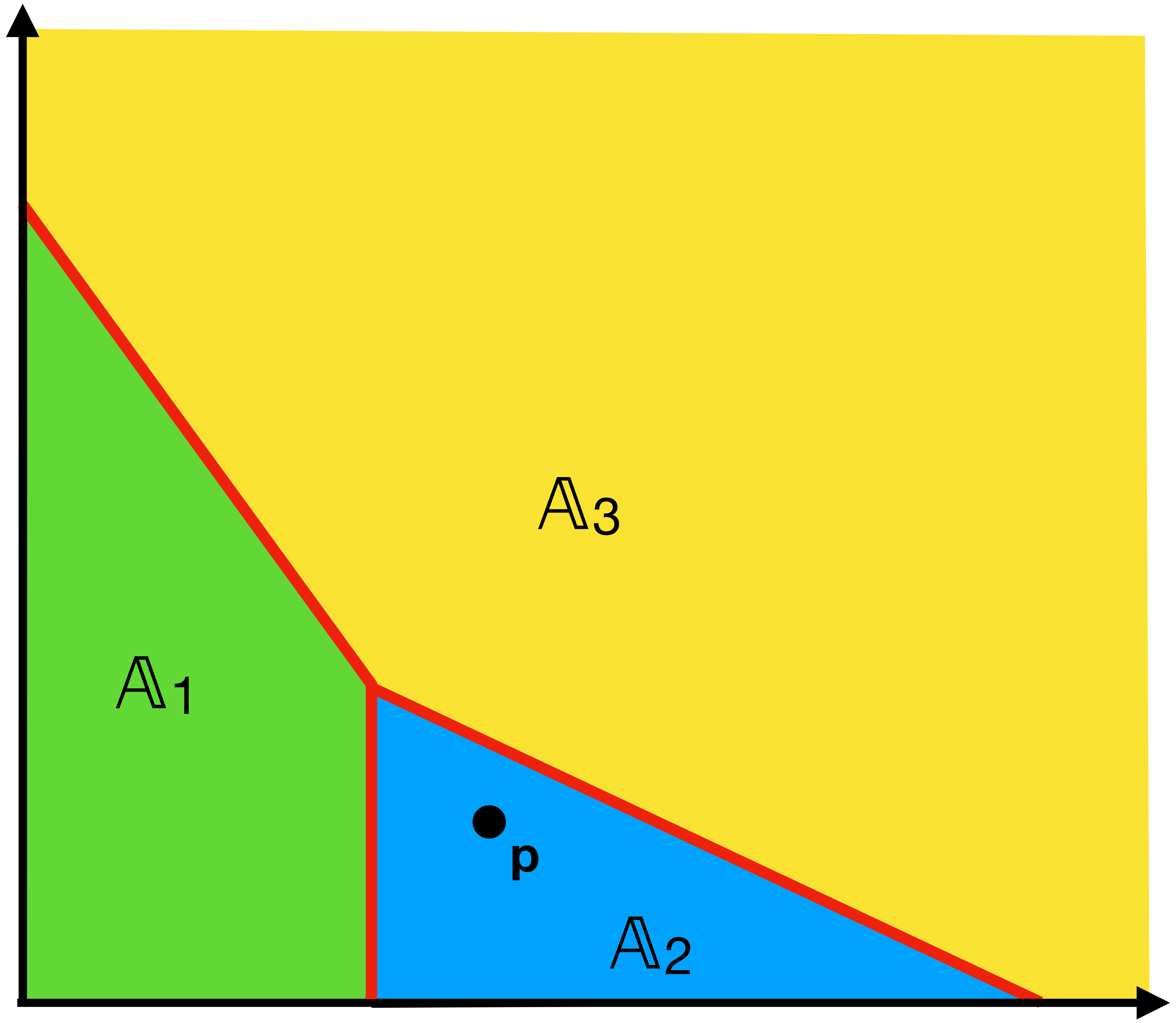
Given two string s_1 and s_2 the (γ, δ)-space decomposes into convex polygons such that any point in the interior of the polygon P is optimal for all points in P



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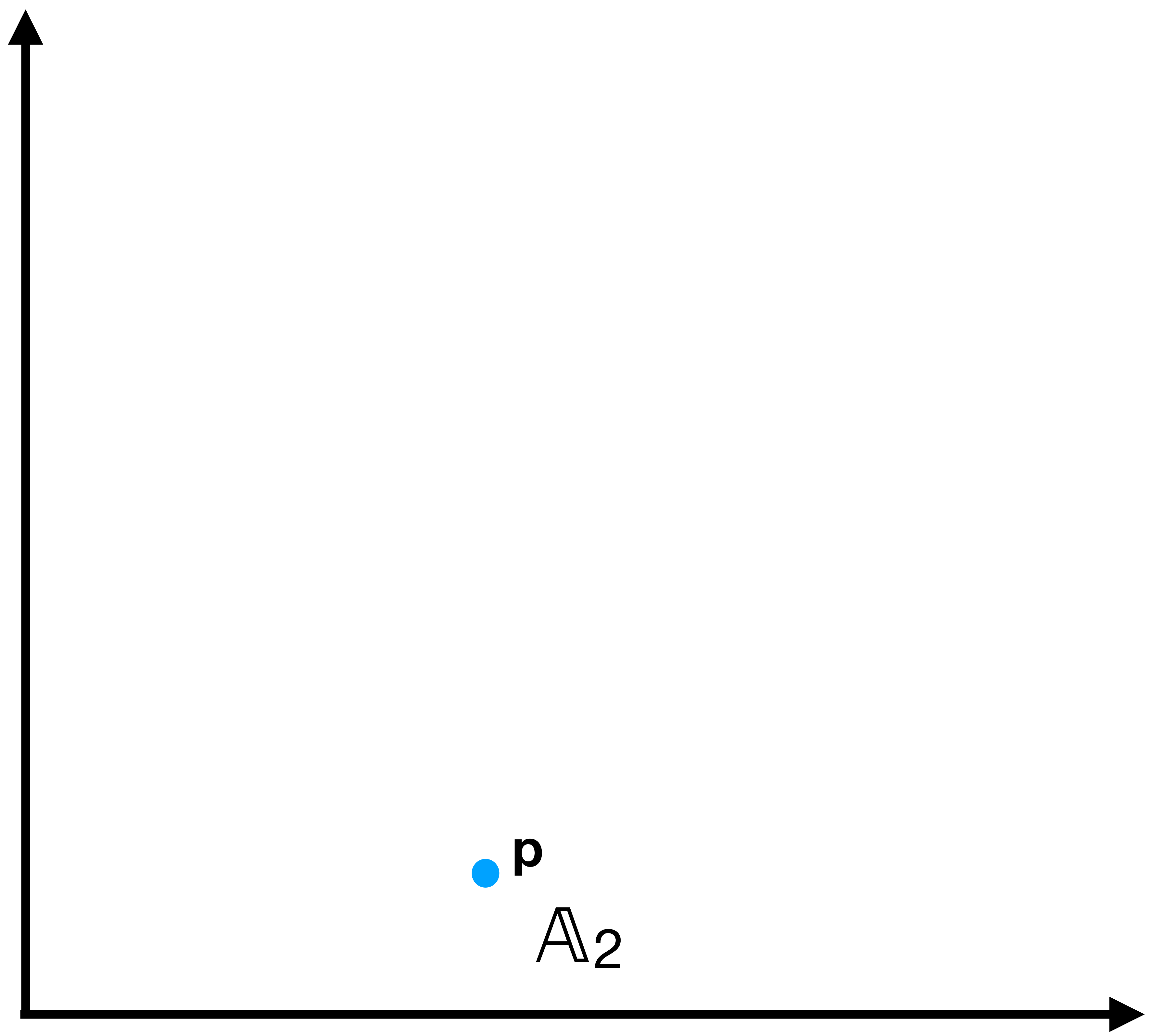
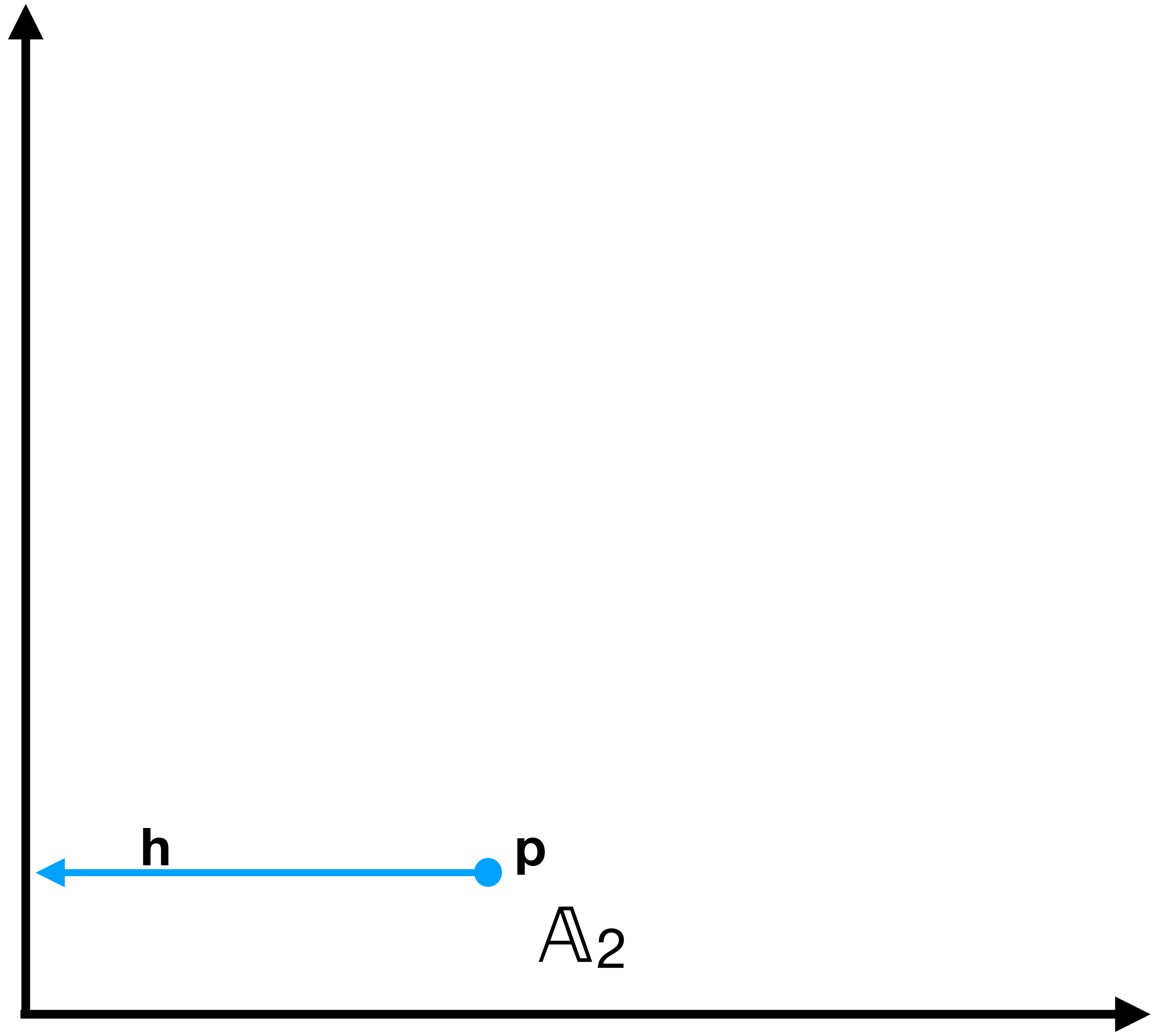
Can we find them?

Newton's ray search algorithm



Newton's ray search algorithm

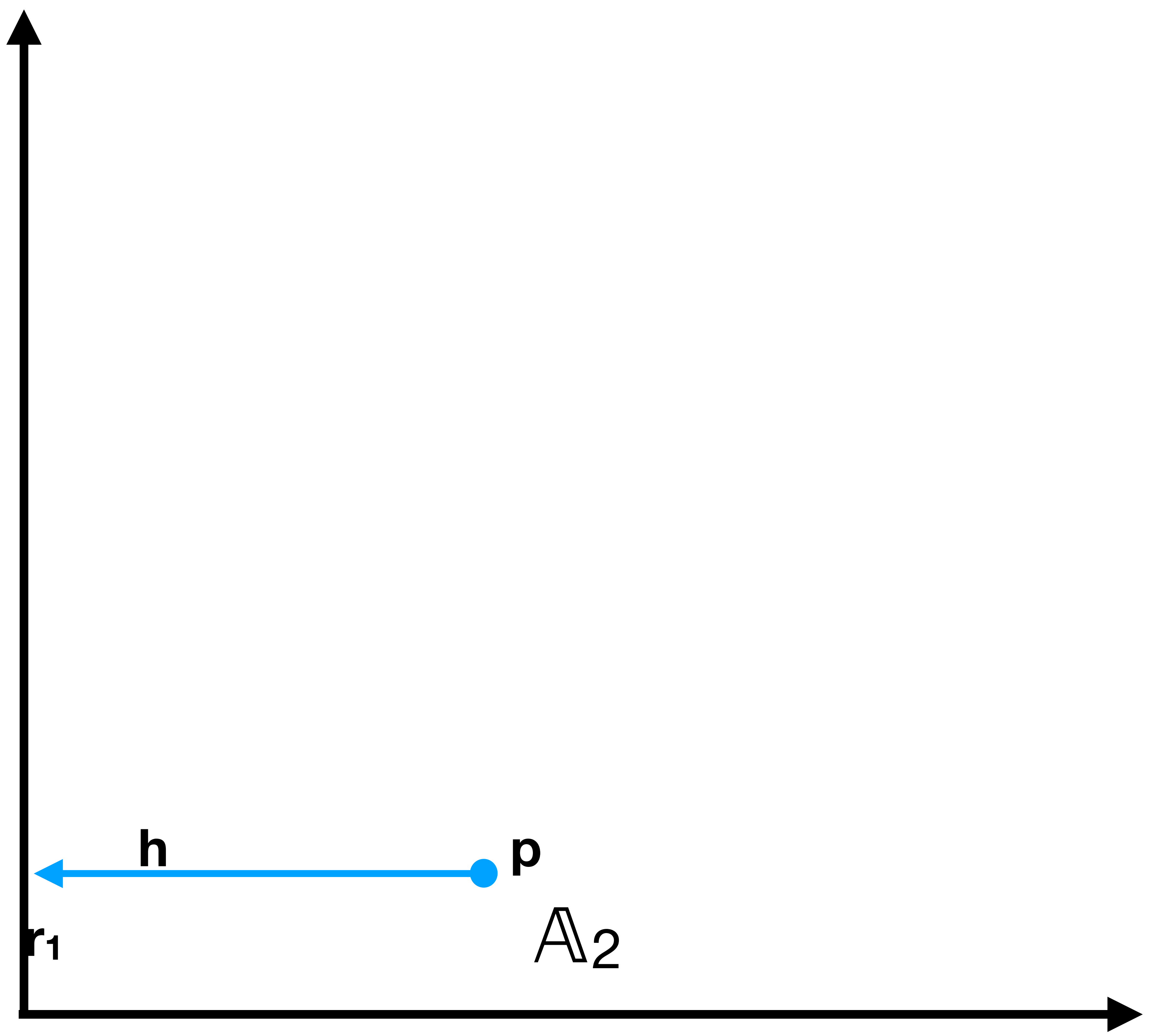
Given a random point p, choose a ray h that extends to the boundary.



Newton's ray search algorithm

Given a random point p, choose a ray h that extends to the boundary.

Let r_1 be the point at that boundary.



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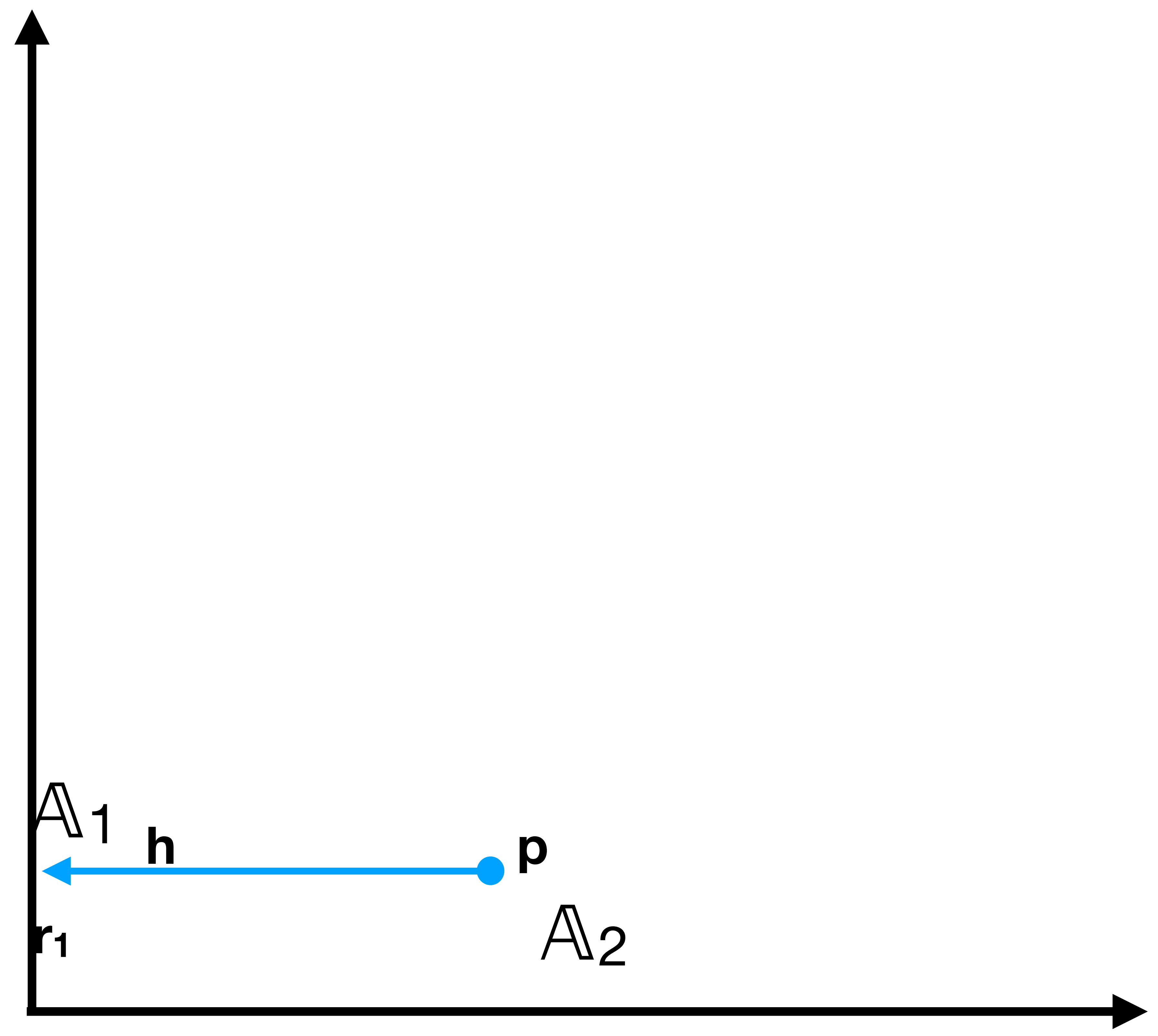
Find alignment $\mathbb{A}'$ that is optimal at r_1.



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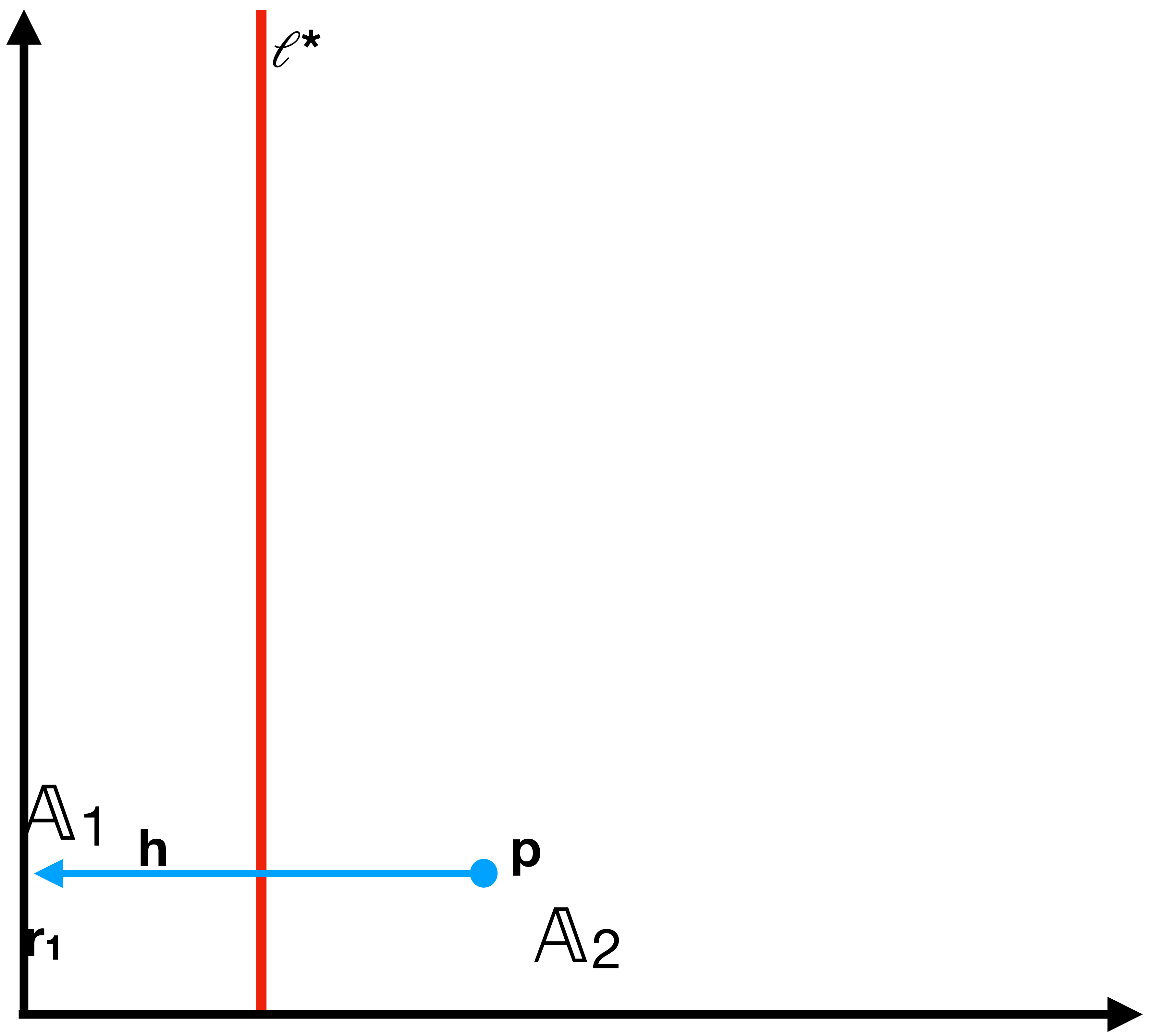
Find alignment $\mathbb{A}'$ that is optimal at r_1.

If $\mathbb{A} != \mathbb{A}'$ let the point r_{i+1} be the parameter choice that is on the line that divides $\mathbb{A}$ and $\mathbb{A}'$, and is also on h.



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Given a random point p, choose a ray h that extends to the boundary.

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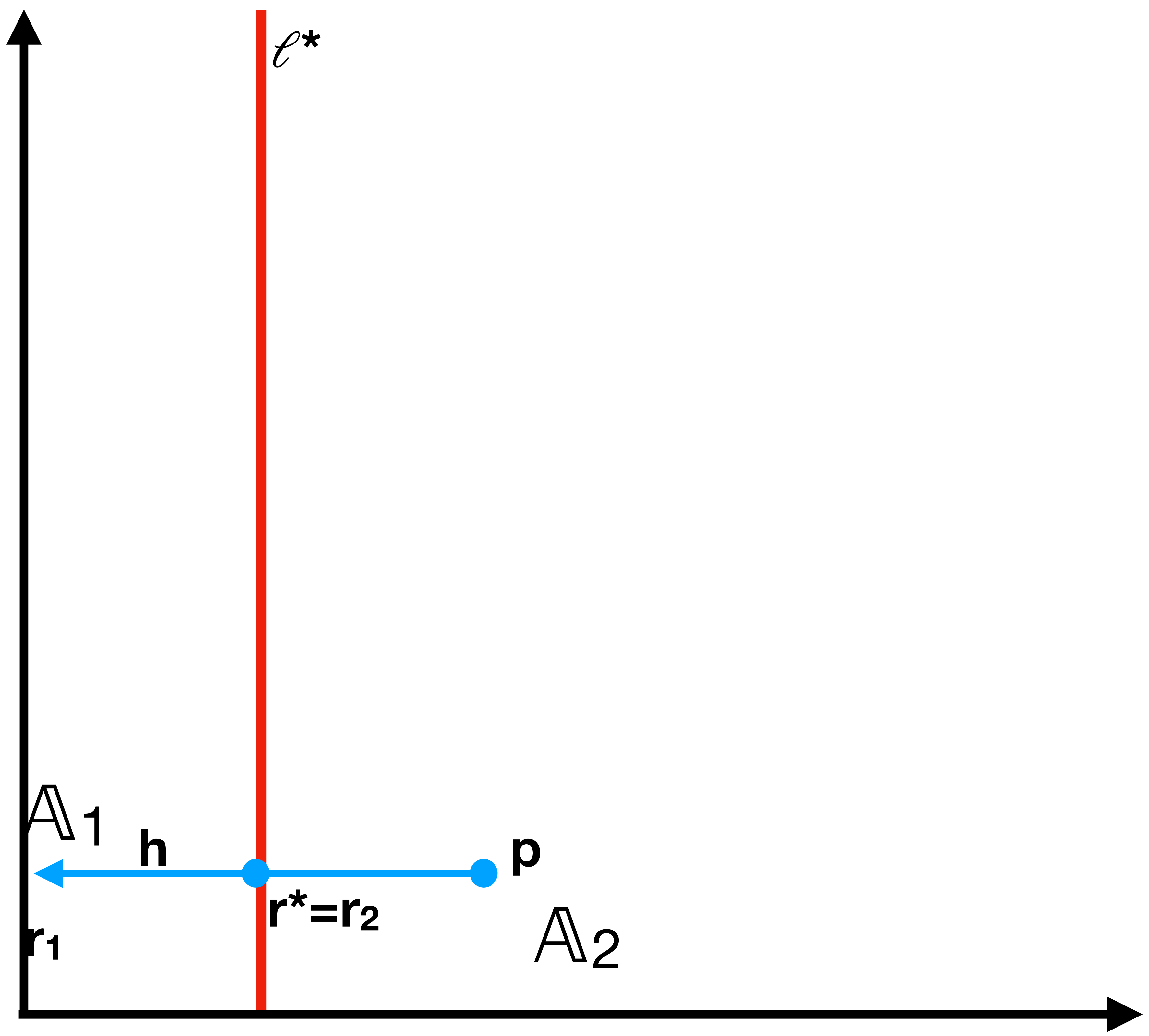
Repeat until $\mathbb{A}$ and $\mathbb{A}'$ are co-optimal (i.e. stop when $\mathbb{A}$ is optimal) at r_{i+1}, and set $r^* = r_{i+1}$.



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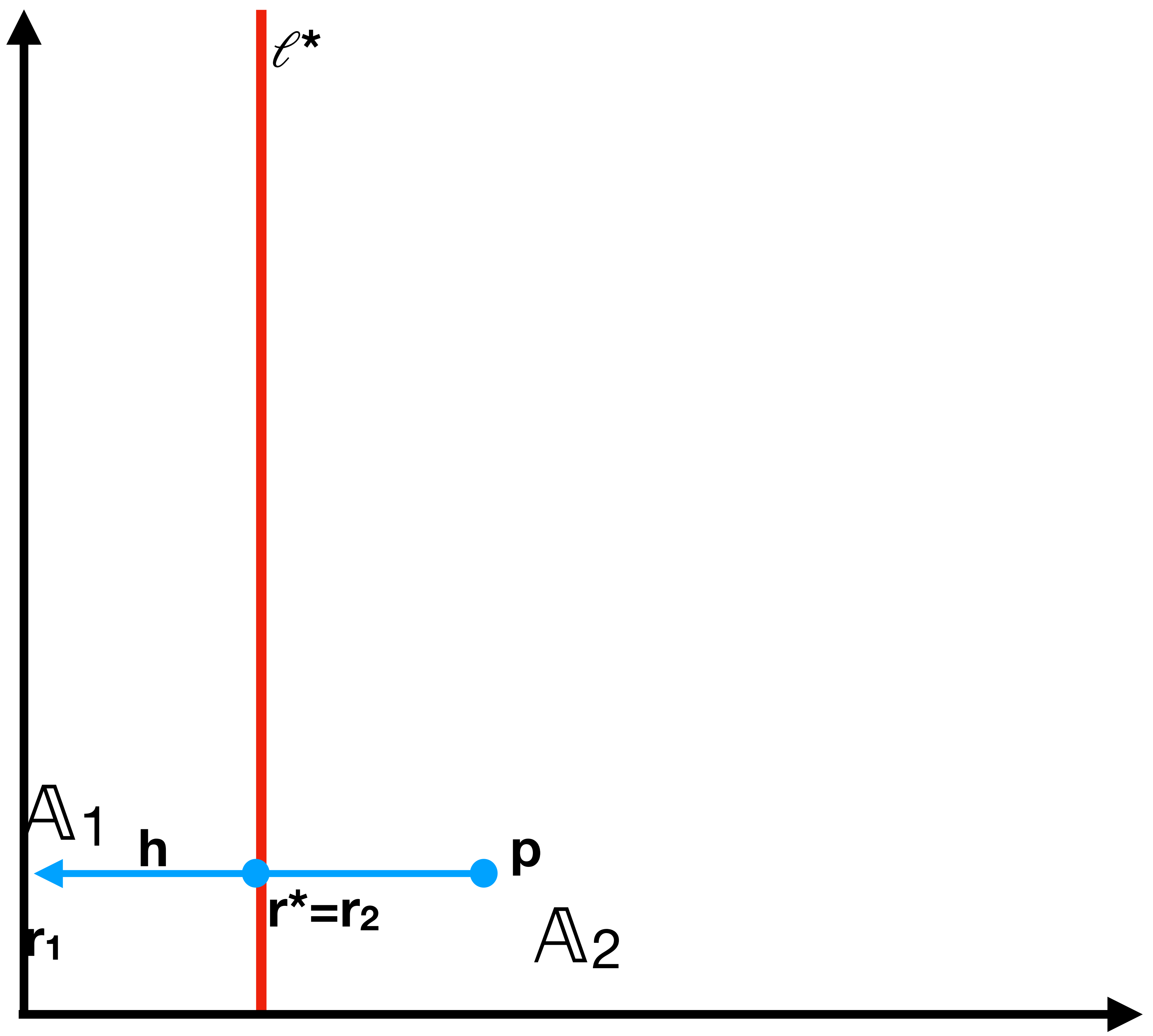
The boundary for the polygon in which p resides is a segment of that line.



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- Unless $\mathbb{A}$ is optimal at the initial setting of r, the last computed alignment $\mathbb{A}^*$ is cooptimal with $\mathbb{A}$ at r* and it is also optimal on h for some non-zero distance beyond r*.

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- When Newton's ray search algorithm computes an alignment at a point r on h, none of the alignments computed previously (in this execution of Newton's algorithm) are optimal at r.

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note: it follows that any polygon P intersected by h, a single ray search computes alignments at no more than 2 points of P.

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Given a point and a ray, we can find a point (and a line) that is at the boundary for the polygon p is in (if it is inside a polygon).

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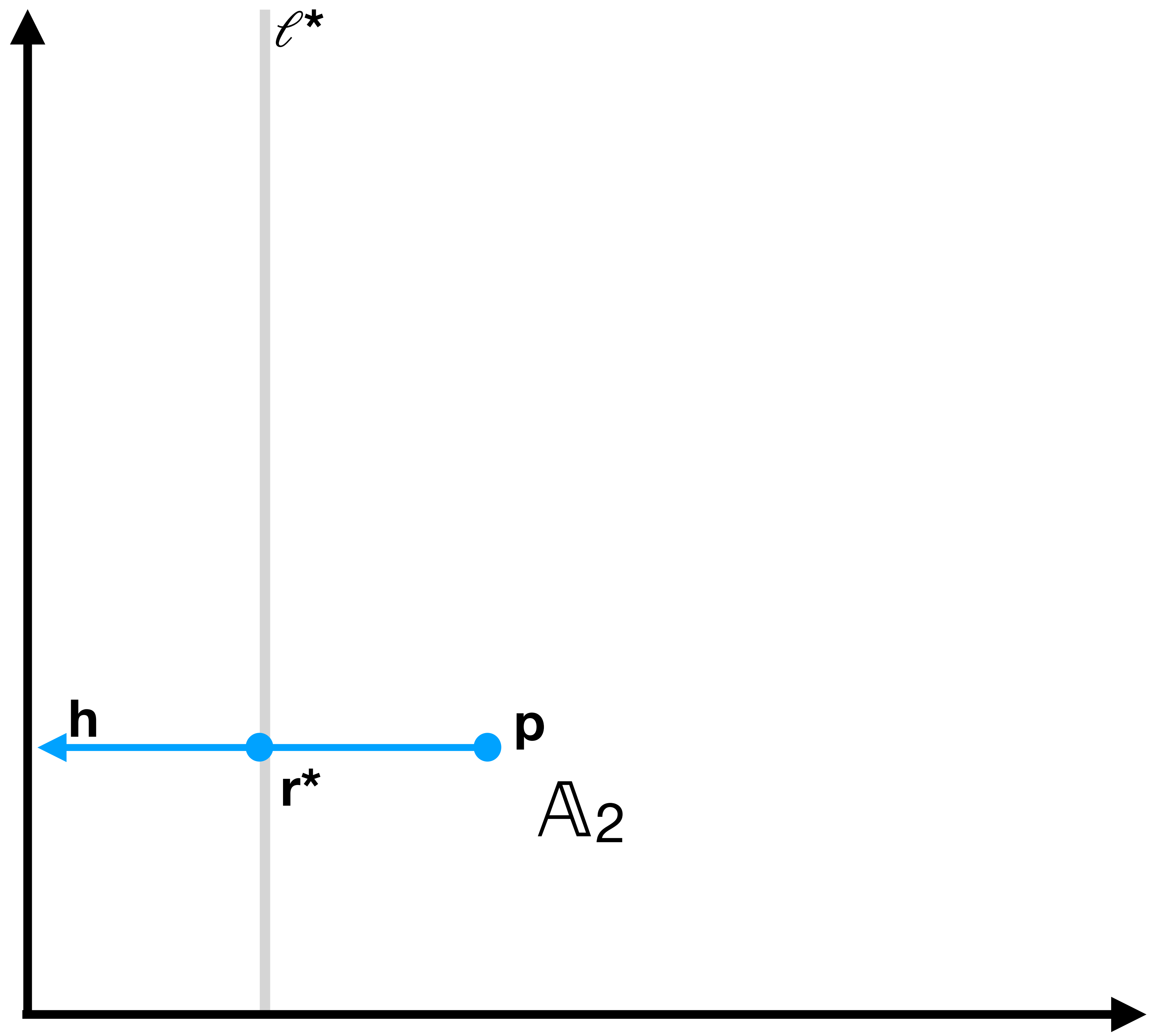
Finding an edge of the polygon

Given p, h, r*, and the line that separates $\mathbb{A}$ from the next optimal alignment on h. (assume p is inside a polygon)



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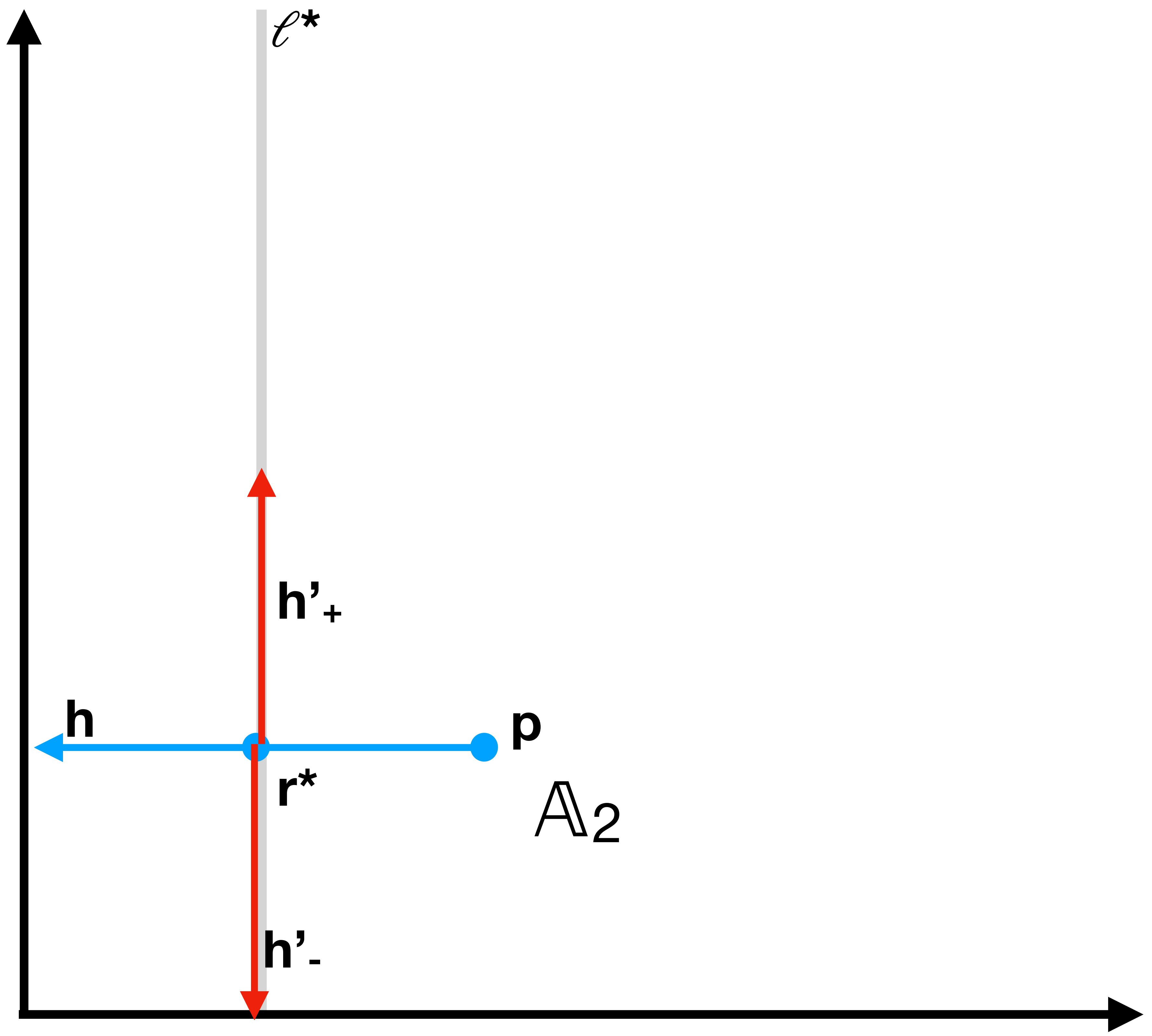
Perform a ray search in both directions from r*, along the line.



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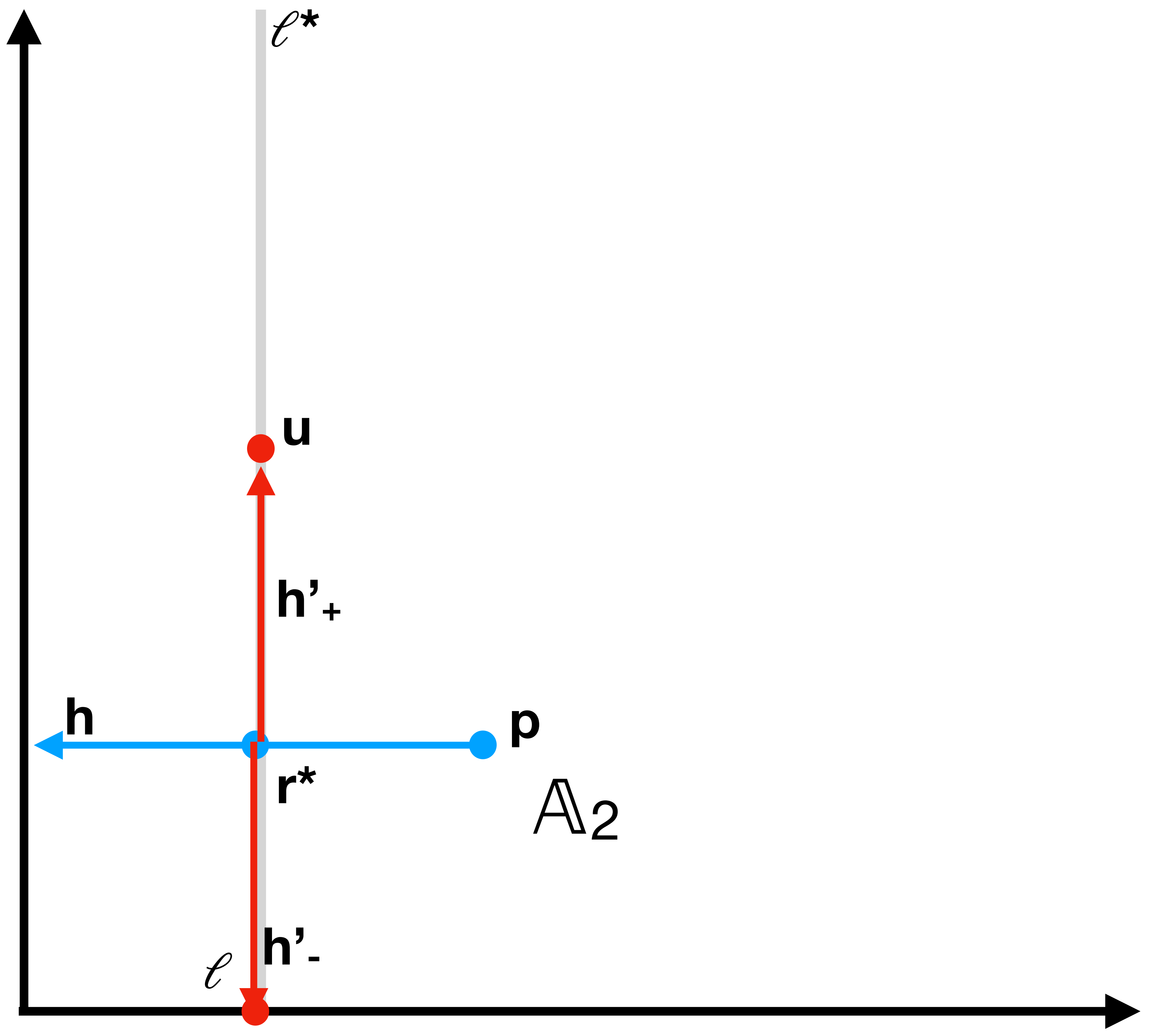
Let l and u be the boundaries where 𝔸 is still optimal.



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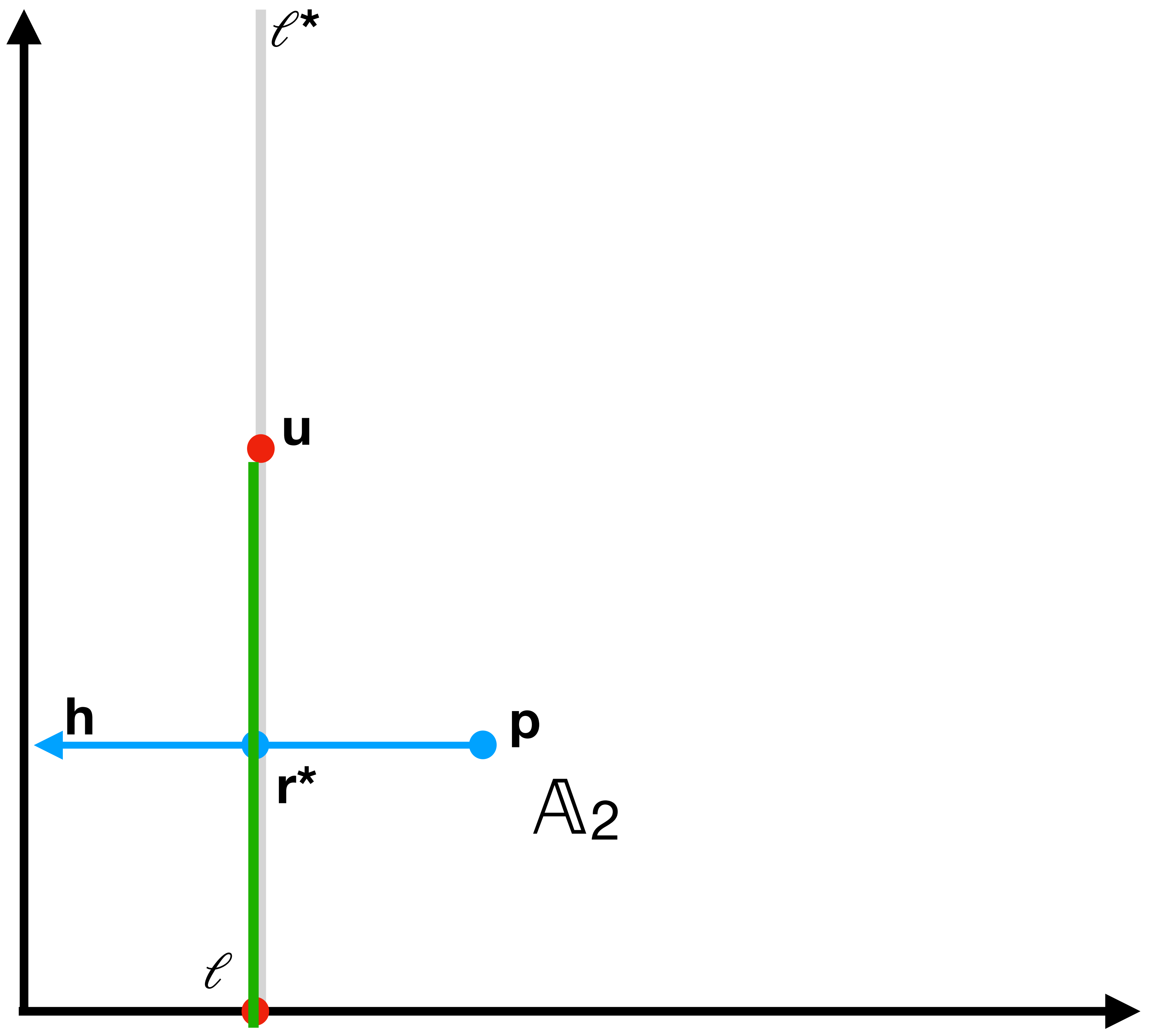
Perform a ray search in both directions from r*, along the line.

Let l and u be the boundaries where $\mathbb{A}$ is still optimal.

The line segment (l,u) is a face of the polygon for $\mathbb{A}$.



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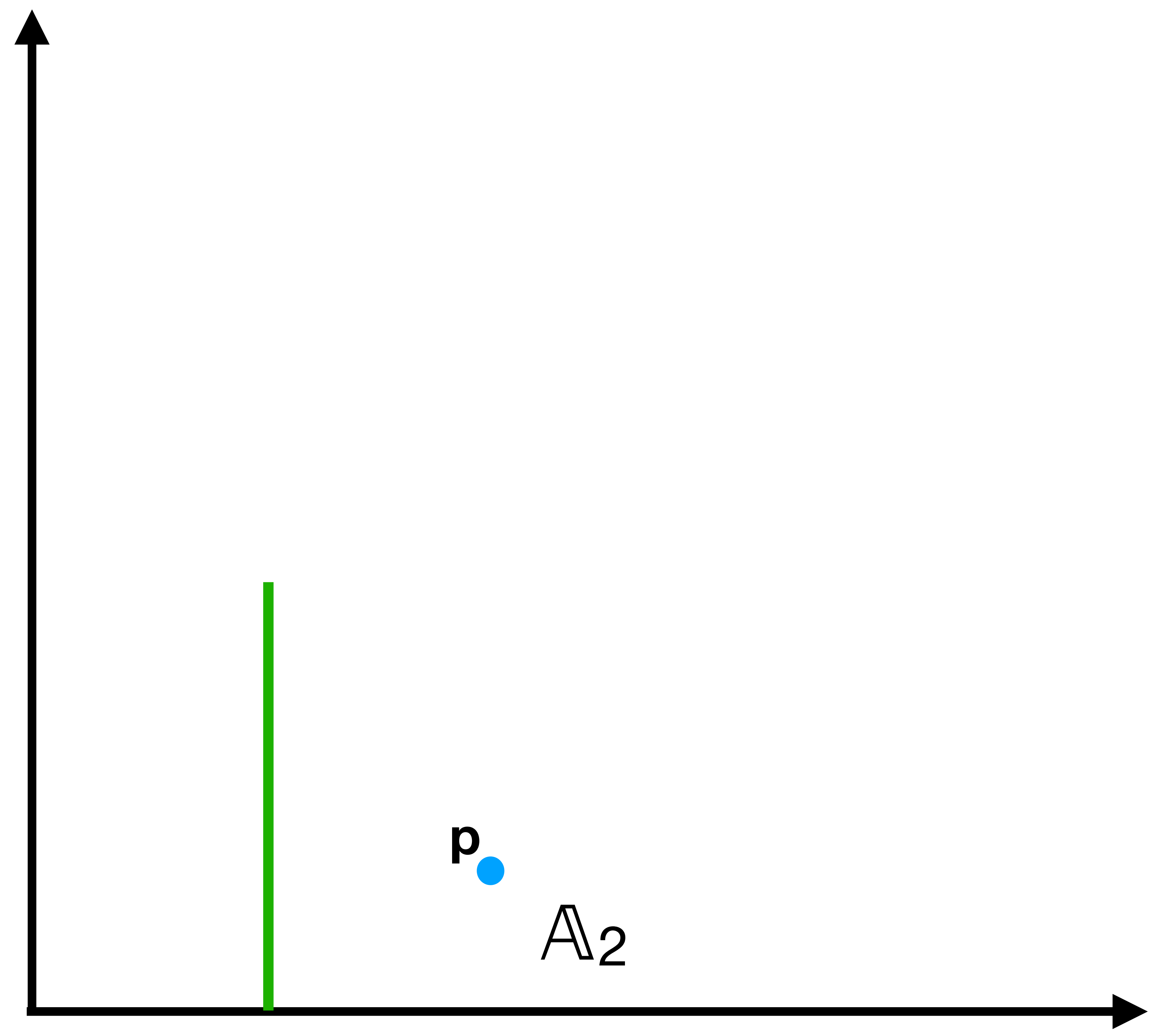
How many regions are there?
Can we find them?

Finding other faces

Given a point p, and a subset of the faces of the polygon in which p resides. (assume p is inside a polygon).



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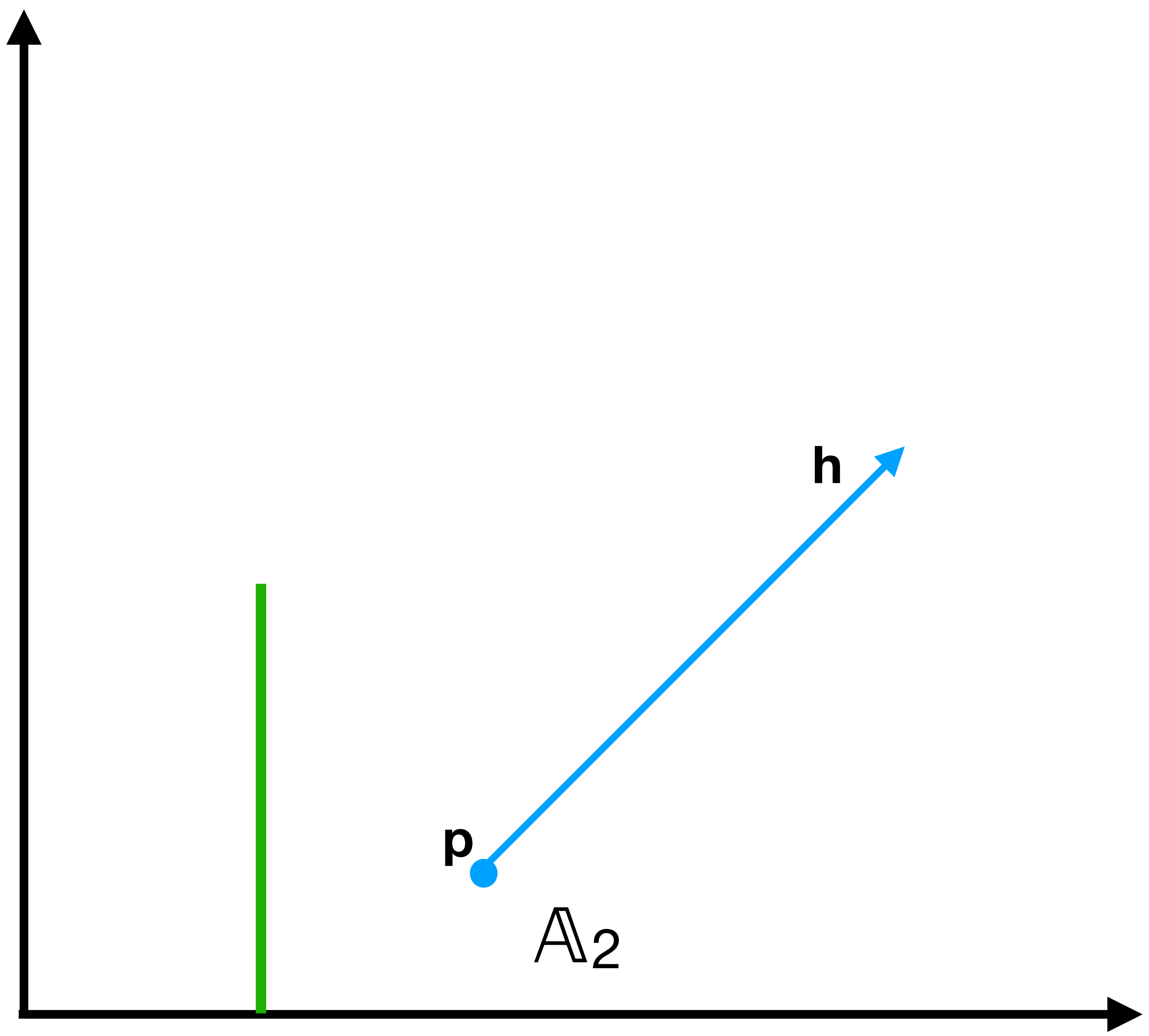

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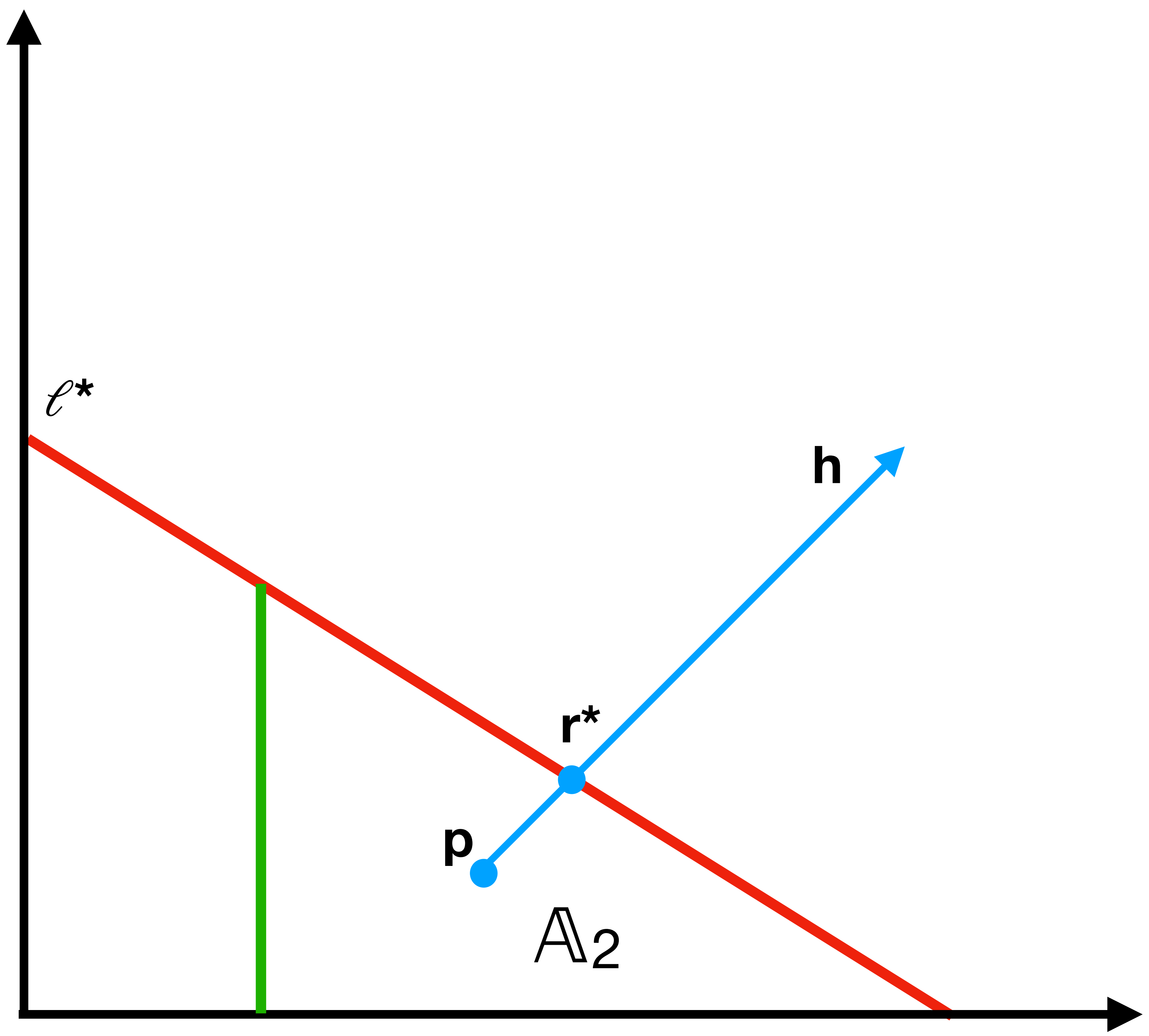
Apply the ray finding algorithm to find r*.



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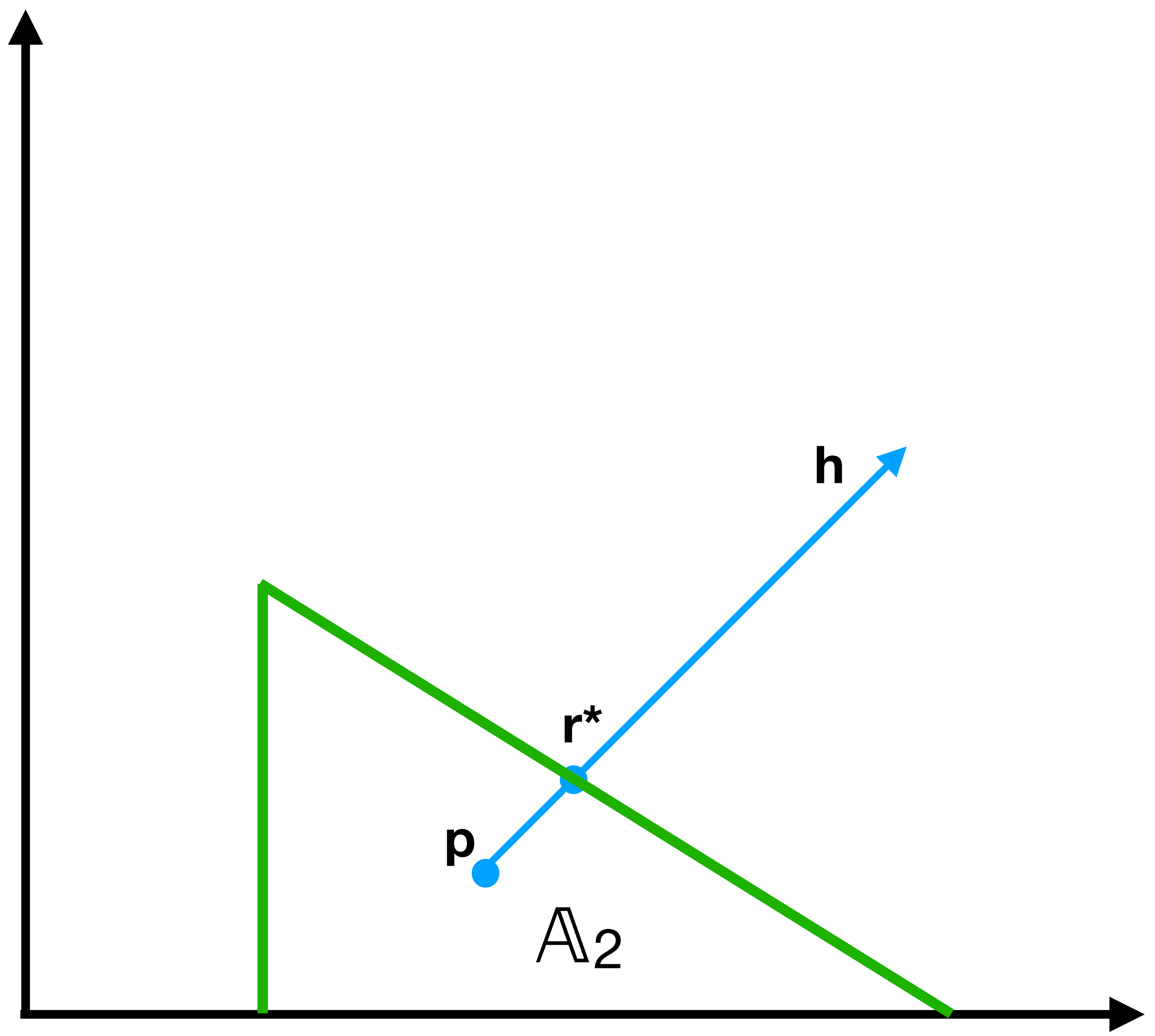

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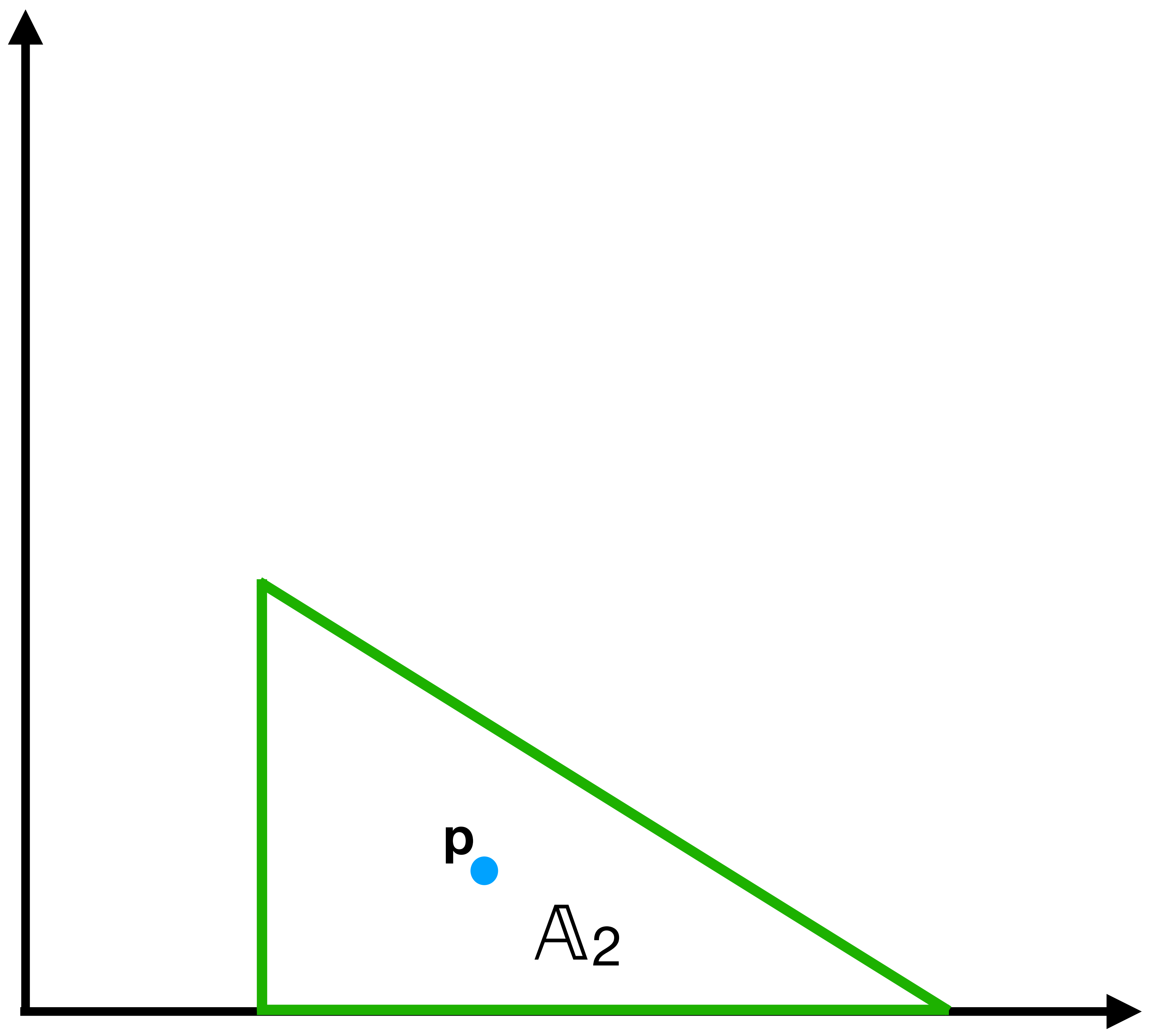

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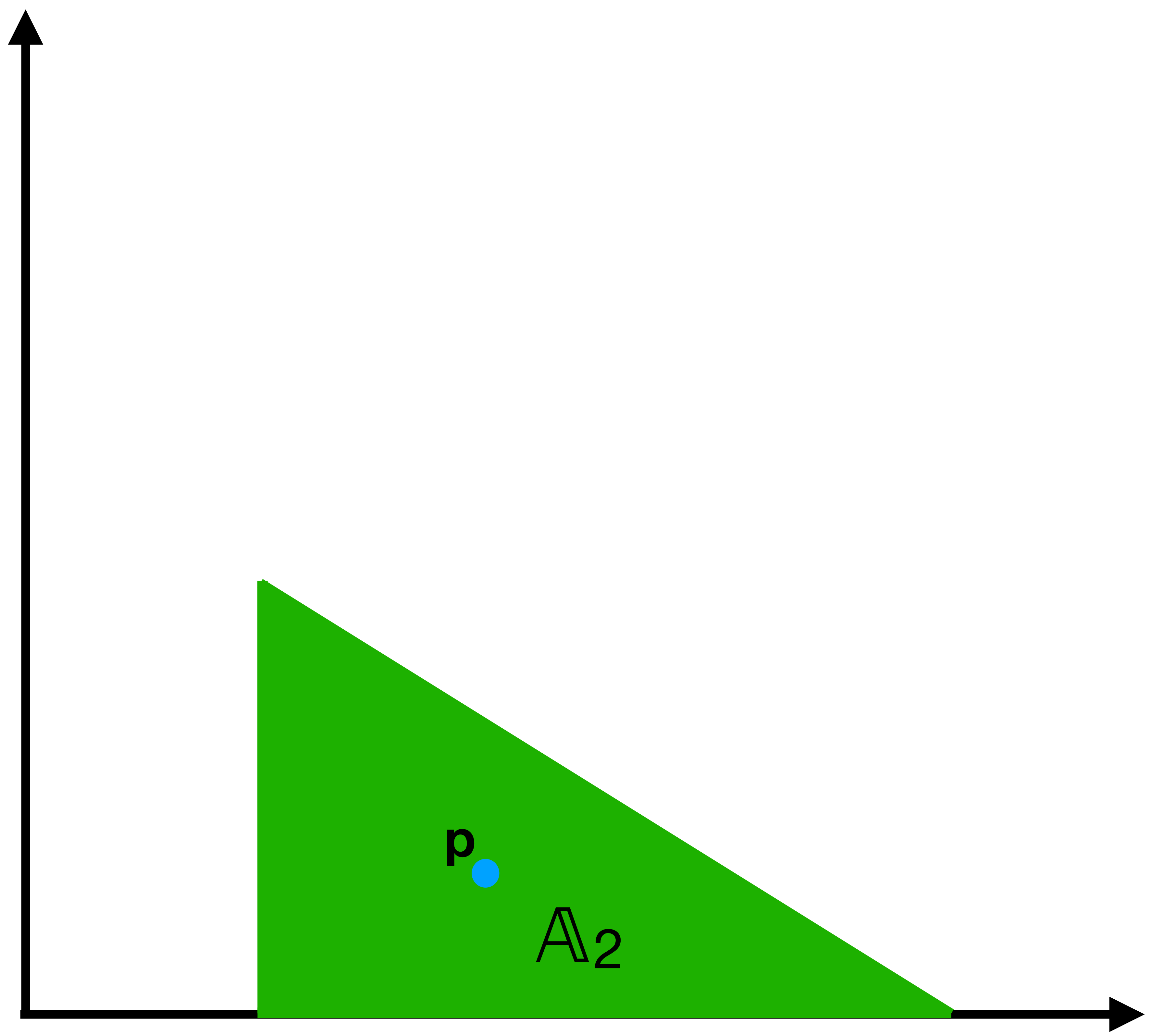

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r* is on the border of the parameter space

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r* is a vertex of the polygon

- one of the ray searches along l* will not find any point beyond r*.
- Stop and use another h that avoids the current r*.

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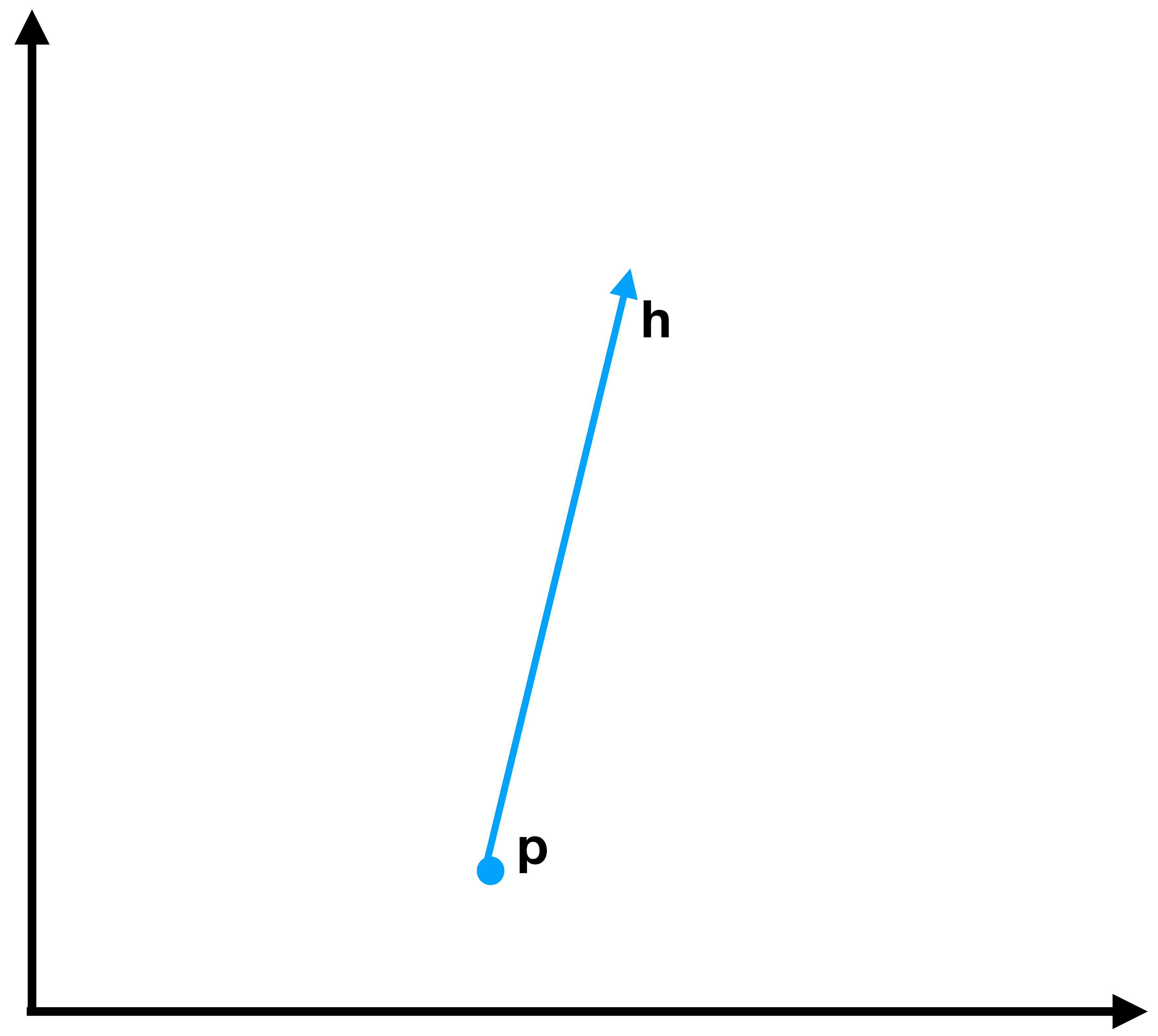

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How do we ensure that a point is on the interior of a polygon?

If r*=p --- $\mathbb{A}^*$ is optimal for some non-zero distance along h.

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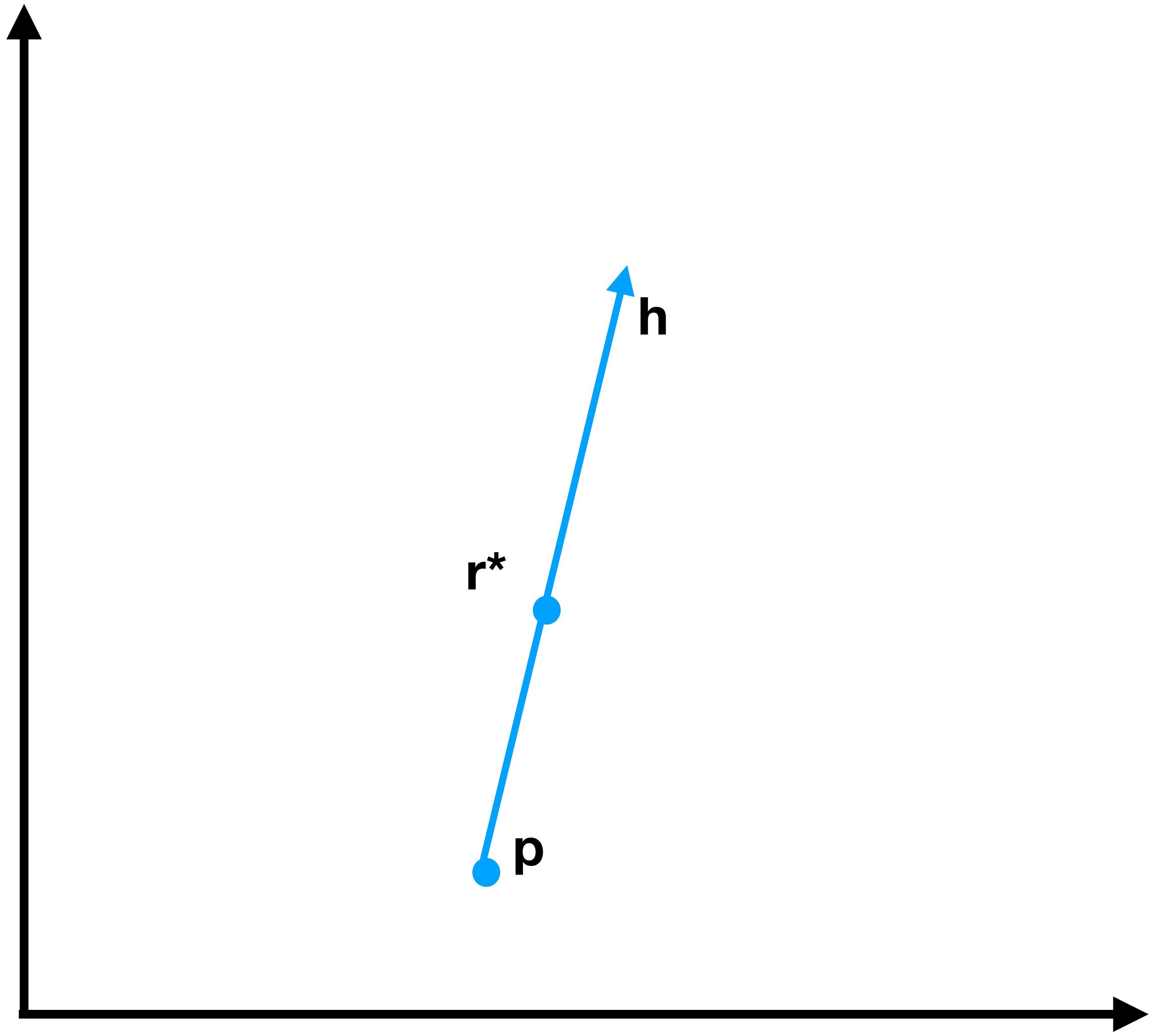

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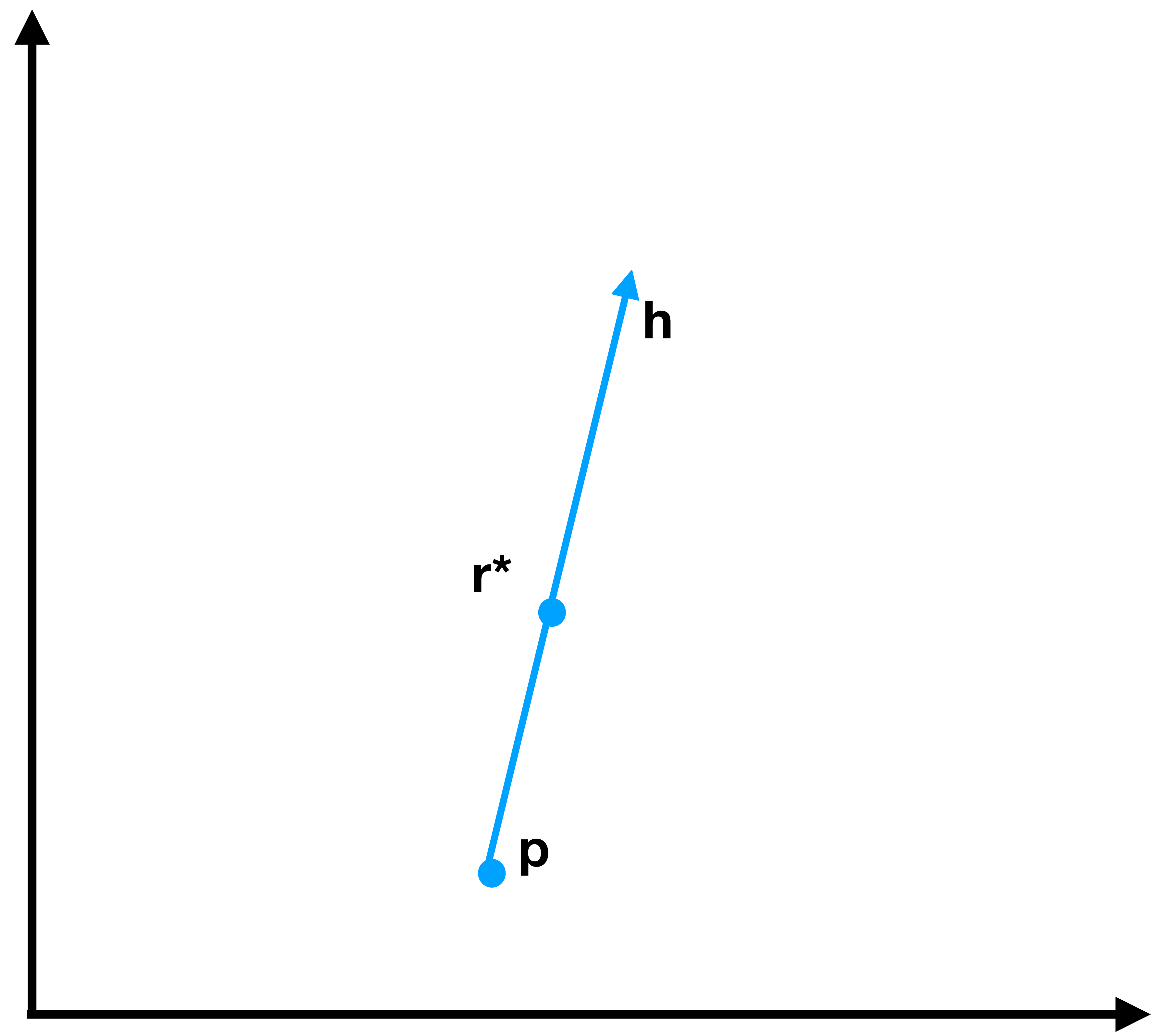

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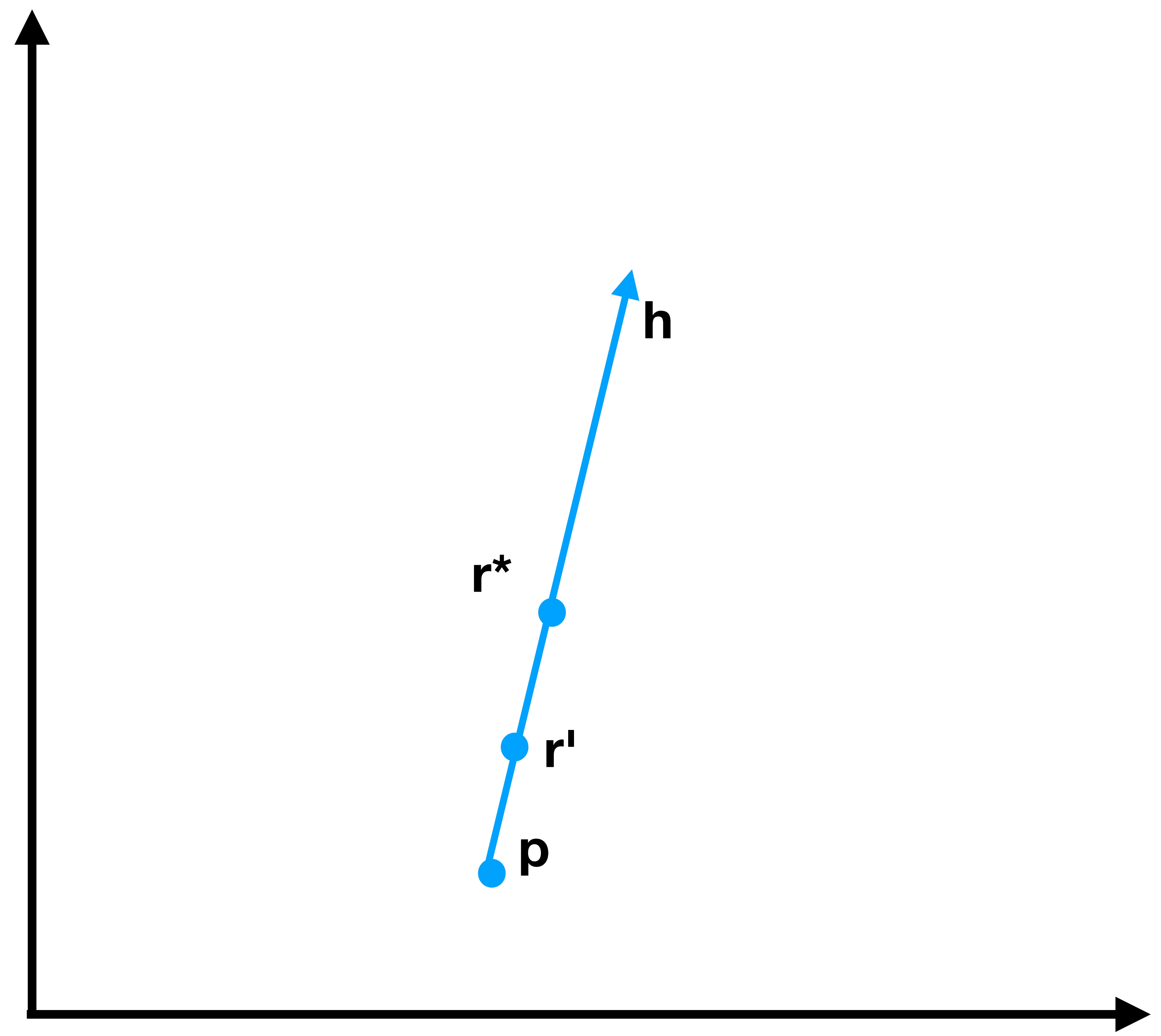

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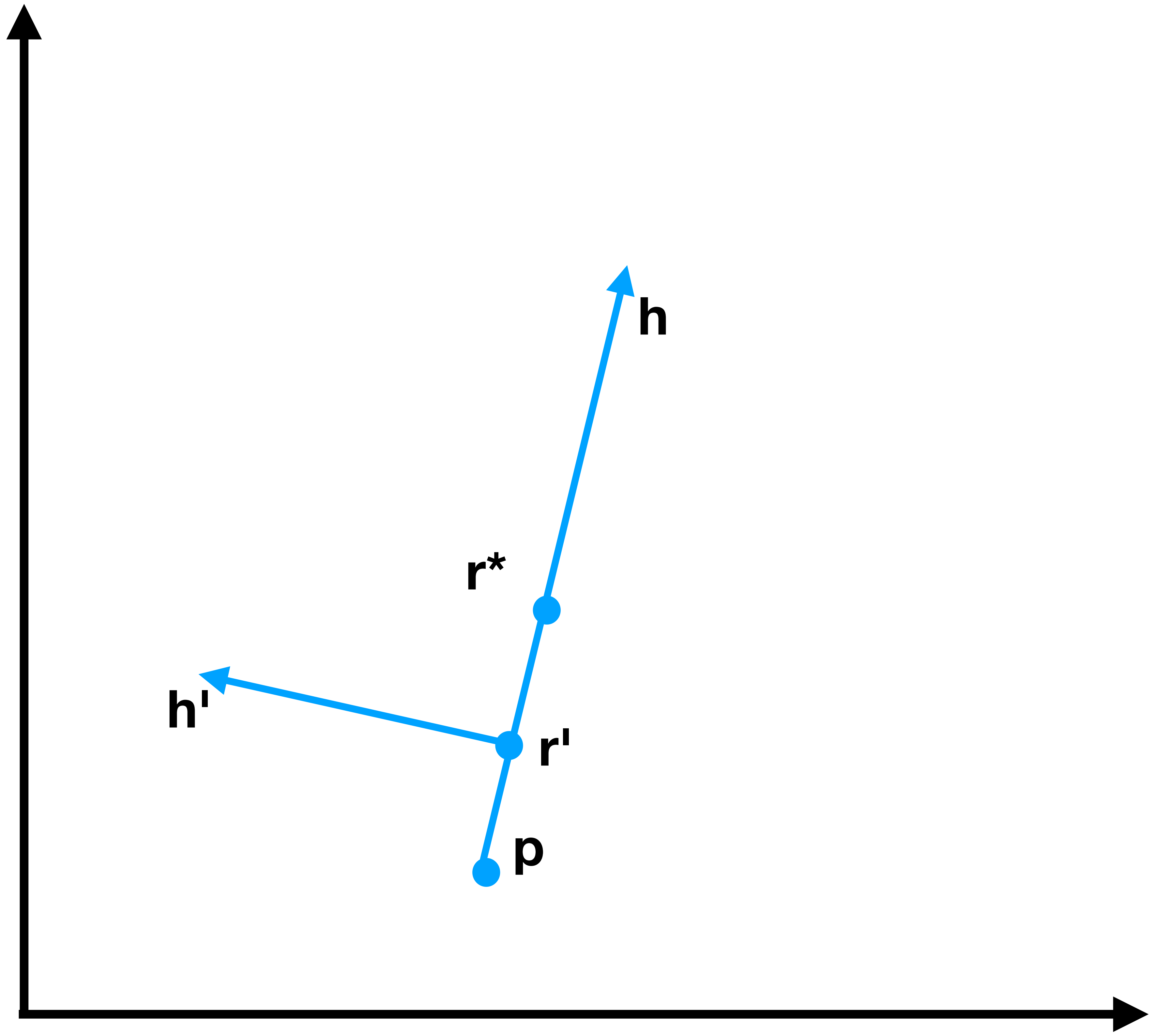

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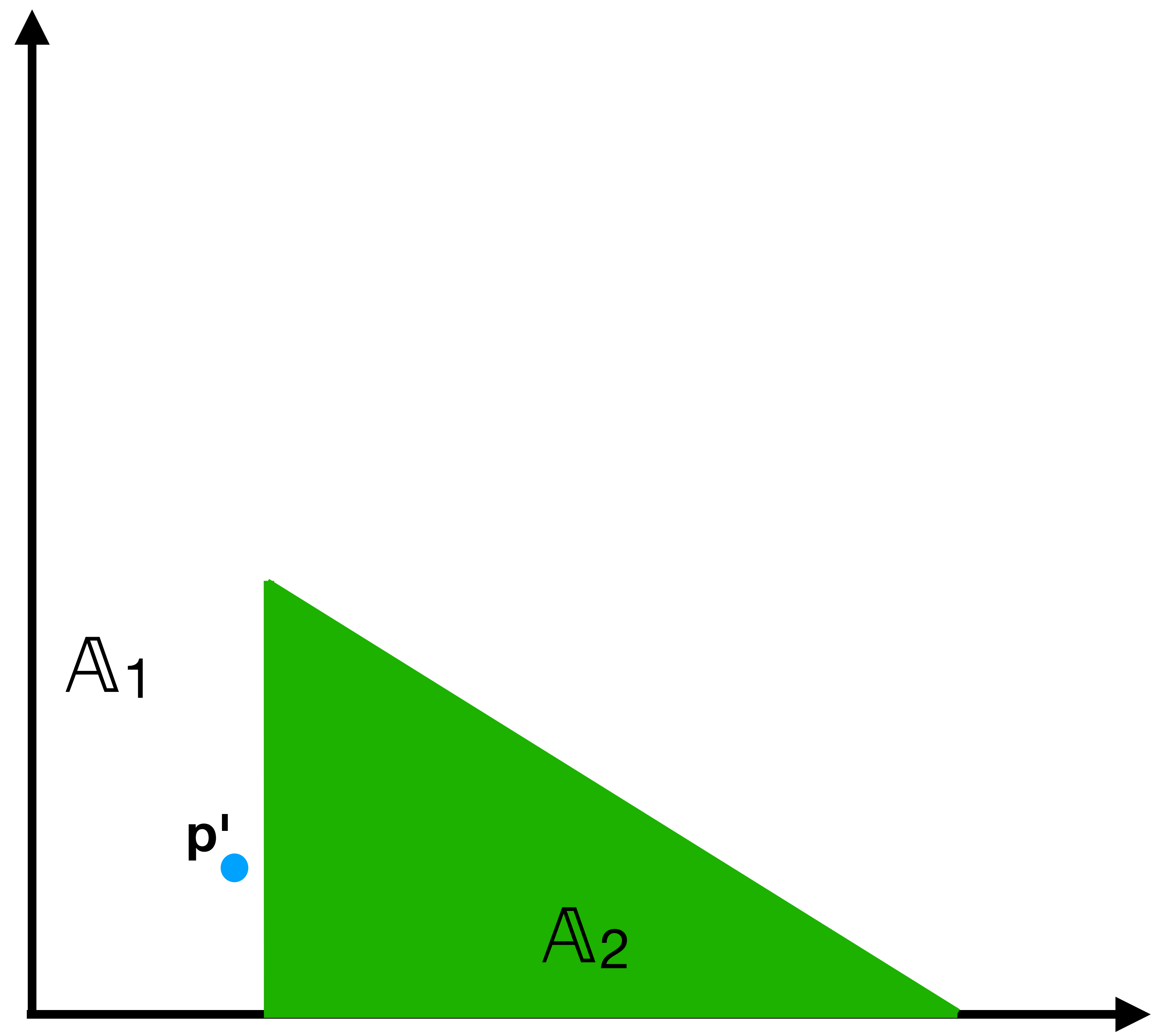

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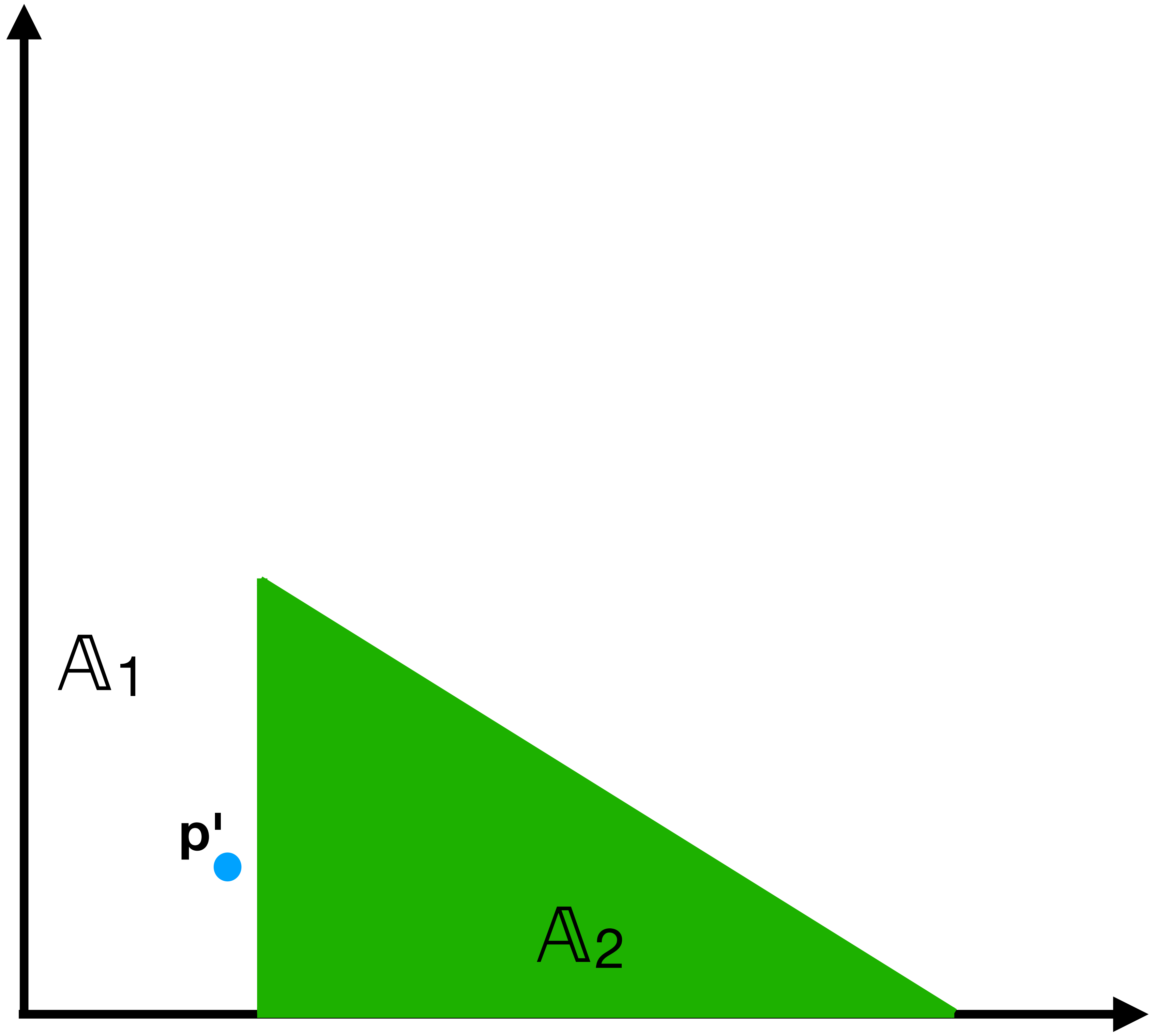

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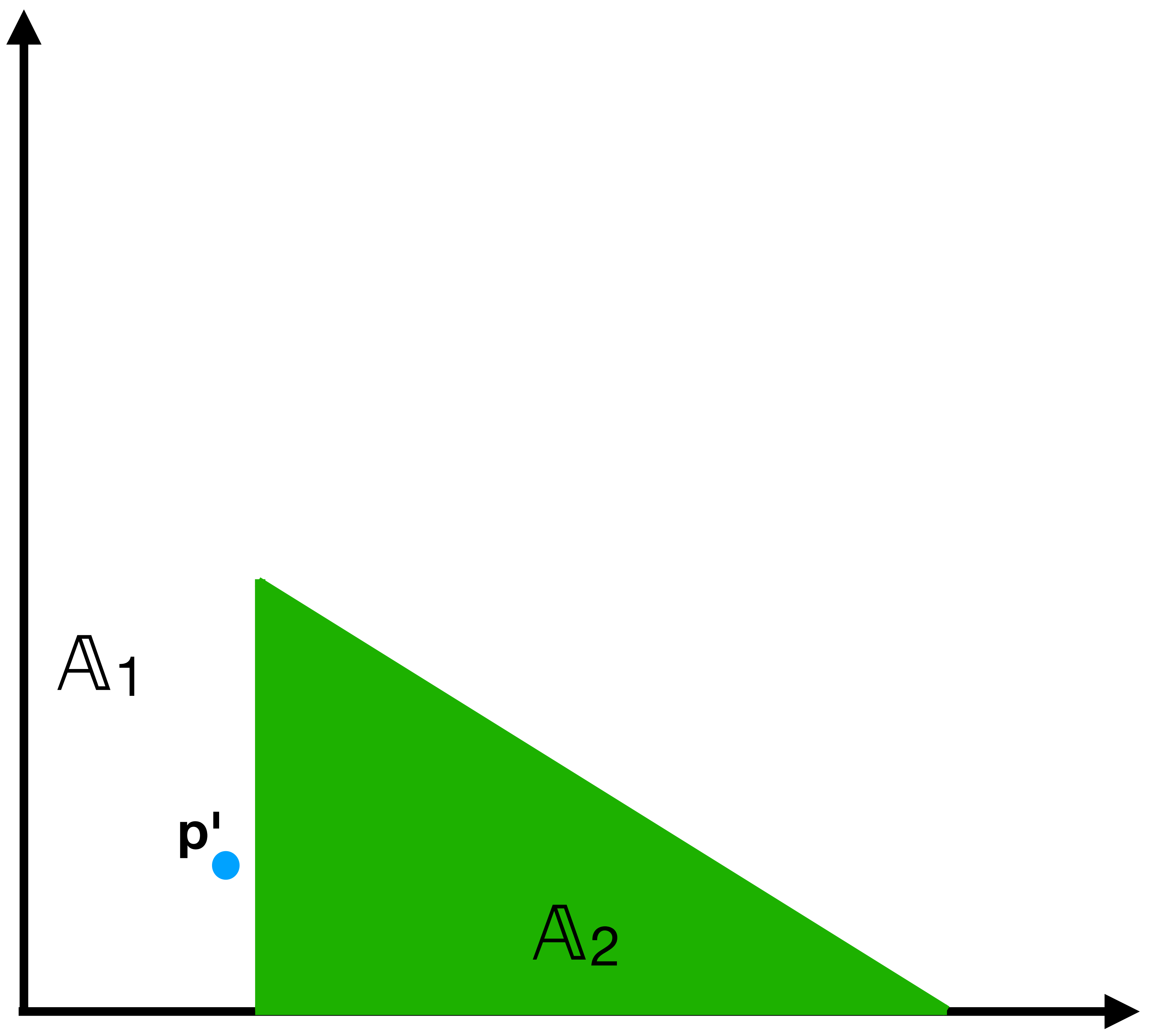

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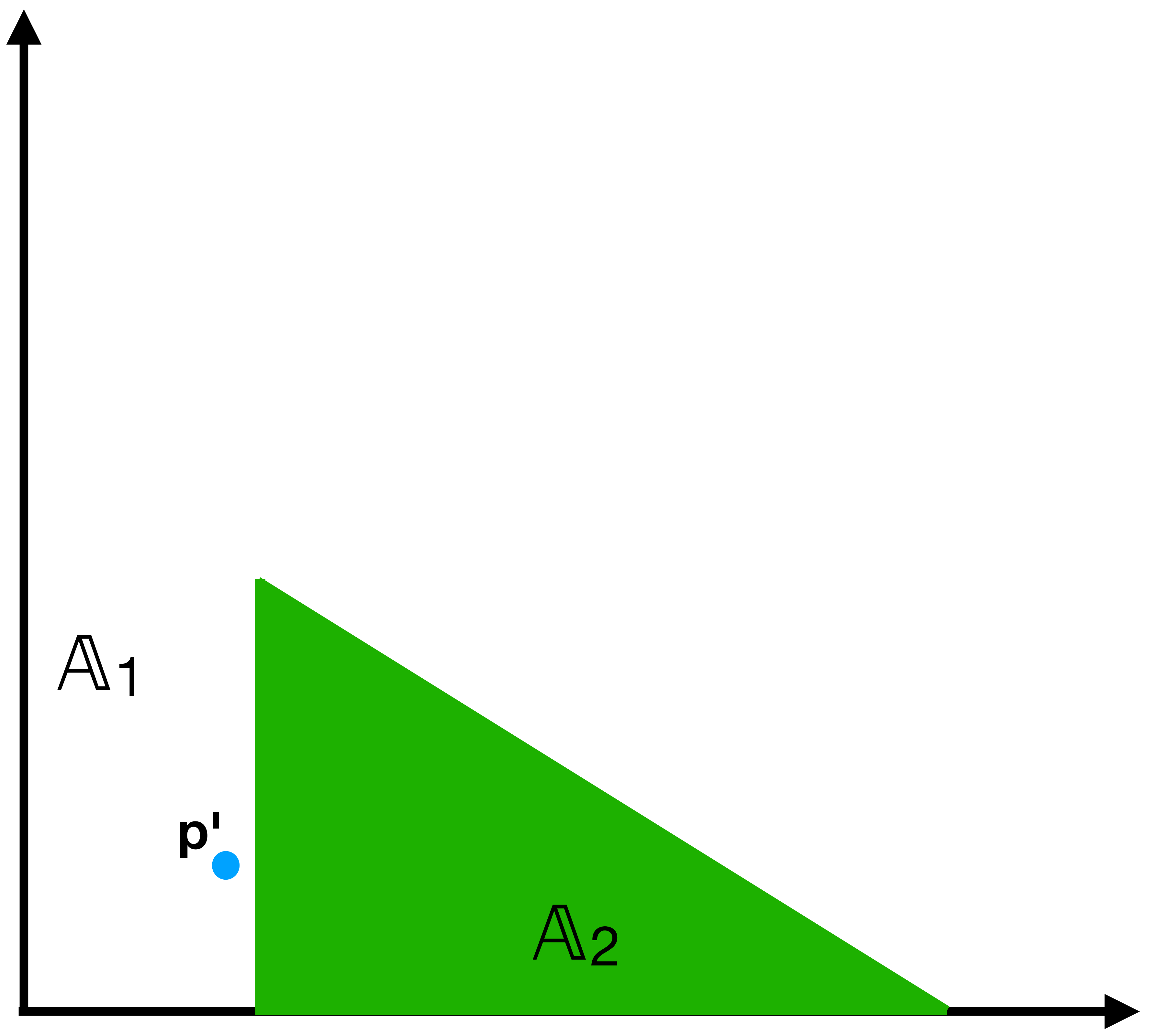

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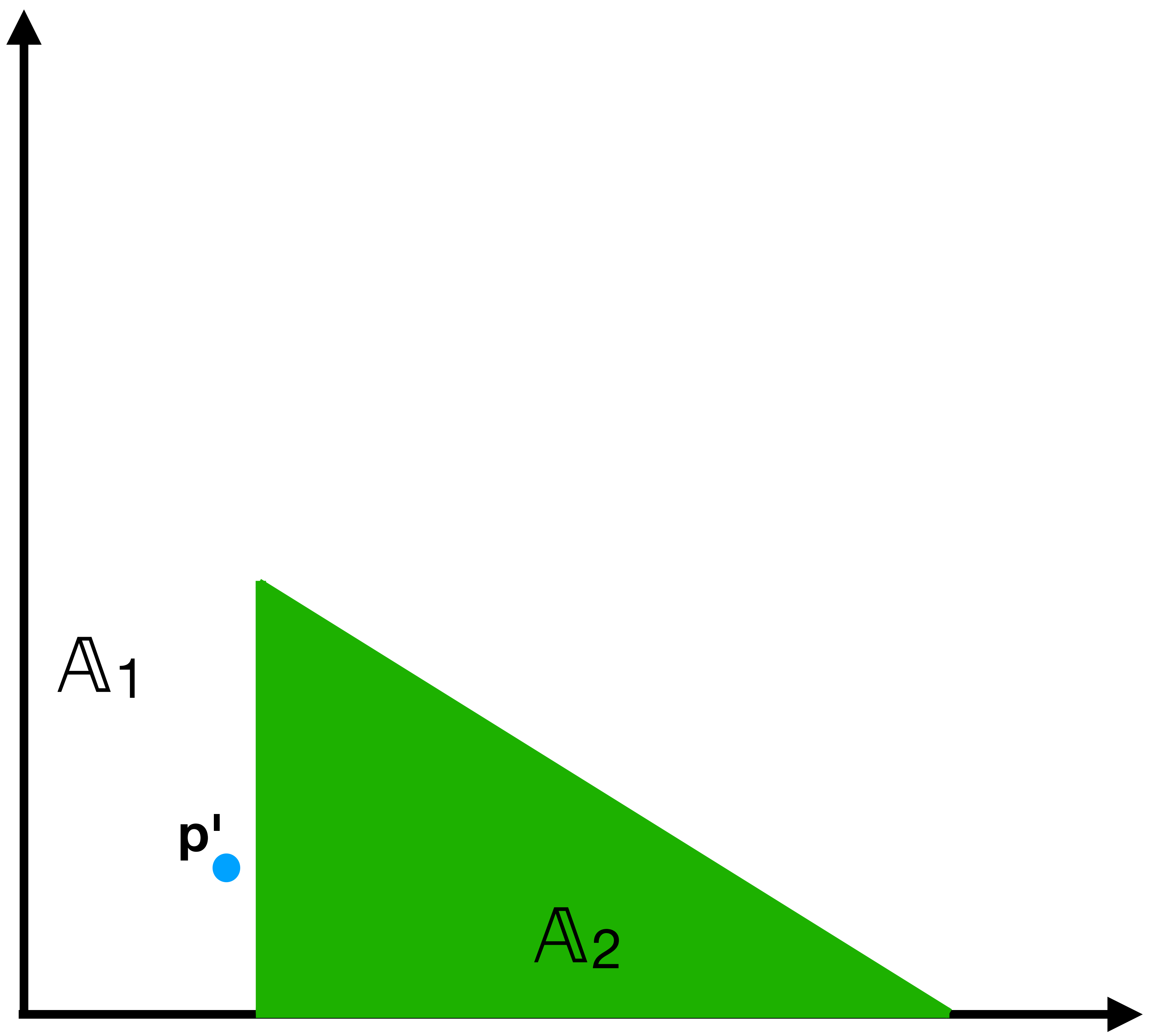

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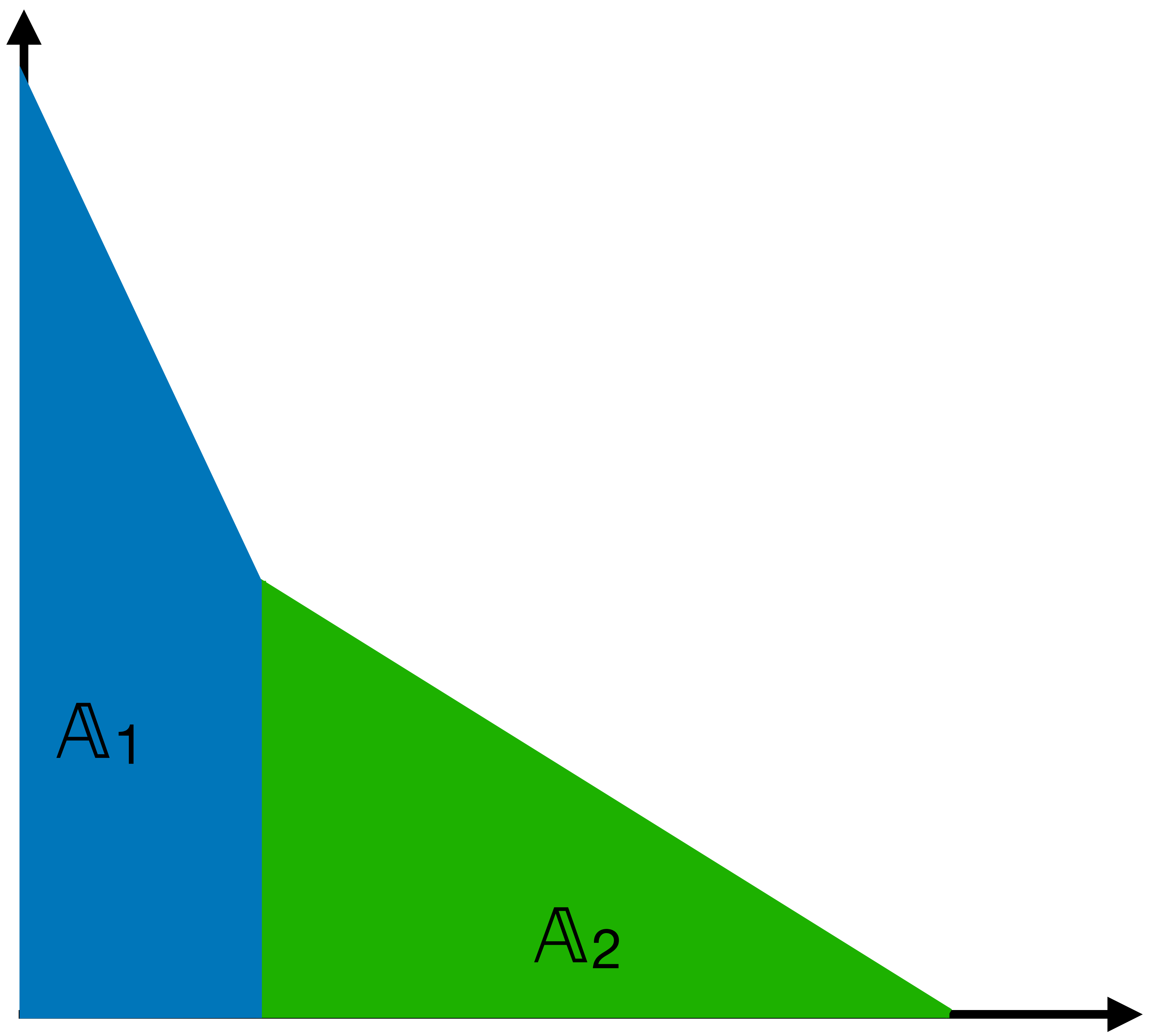

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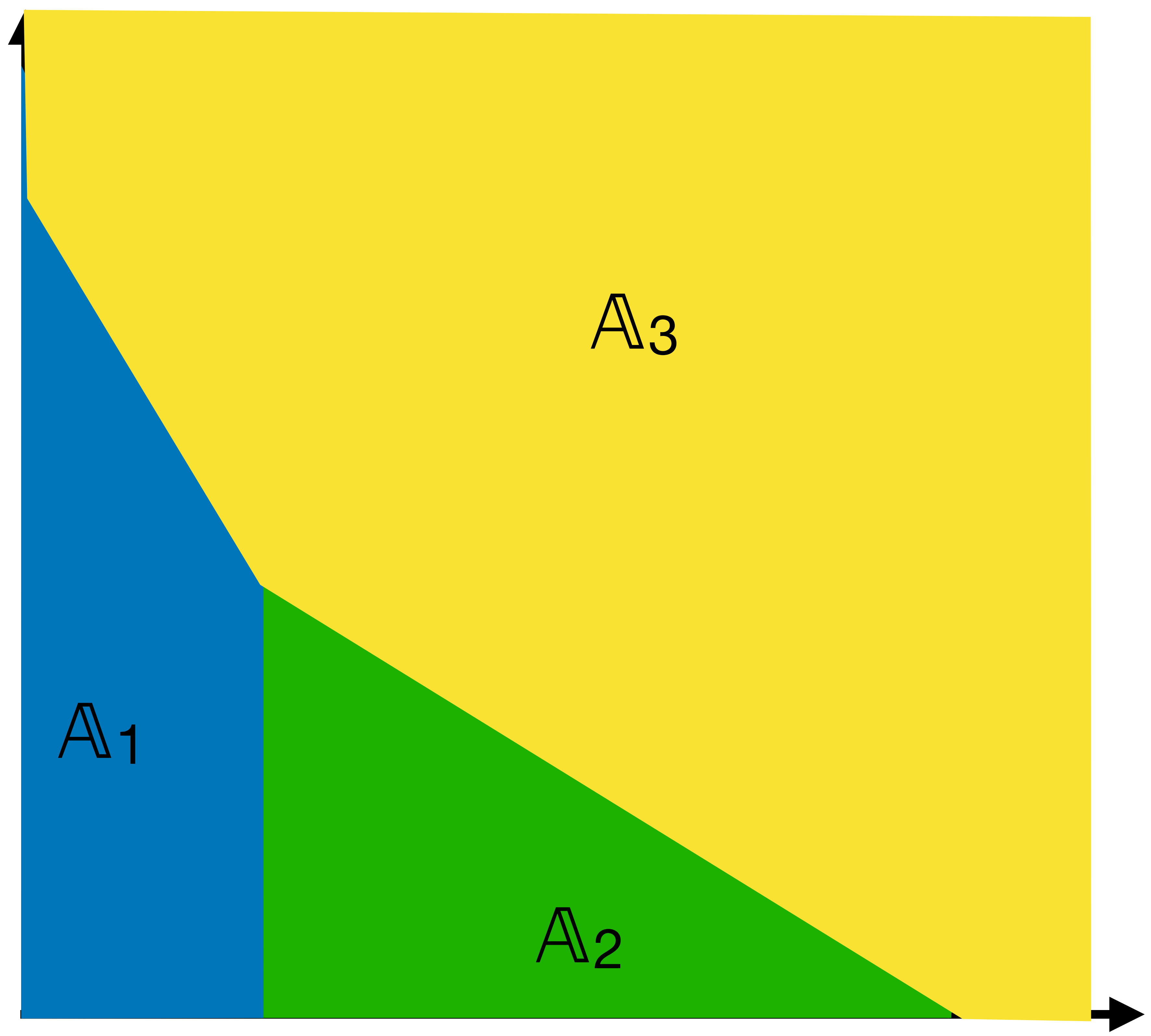
When entire list is marked, the decomposition is complete.



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If $n \le m$ are the lengths of the string, there can be at most m+n gaps, and m+n indels.
Any two alignments with the same triple are optimal at exactly the same points.

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Can be $O(m^4)$!

Decomposition Speed

Keep a list *L* of optimal alignments found along the way (the values of **mt**, **ms**, **id**, & **gp**)

Any time a new *h* is chosen, find the place where the line intersecting the optimal alignment and every alignment in *L* intersect *h*

Start the ray search at the closest to *p* rather than the boundary.

The size of *L* is bounded by sum of the number of vertices (V), edges (E), and polygons (R) in the decomposition.

$O(E)$ ray searches to find all edges, therefore $O(E(V+E+R)) = O(m^4)$ extra work to use *L.*

When doing a ray search, we only compute an alignment for points not in *L*, then they are added to *L*, so the number of alignments is bounded by the same size as *L*, therefore the alignment running time is $O((V+E+R)m^2) = O(m^4)$

Parametric sequence alignment

For a fixed input:

- there are $O(m^2)$ optimal alignments when two parameters are free
- the regions can be found by repeated ray-search

More free parameters

$$f_{\alpha,\beta,\gamma,\delta}(\mathbb{A}) = \alpha \cdot \mathbf{mt}_{\mathbb{A}} - \beta \cdot \mathbf{ms}_{\mathbb{A}} - \gamma \cdot \mathbf{id}_{\mathbb{A}} - \delta \cdot \mathbf{gp}_{\mathbb{A}}$$

- $\mathrm{mt}_{\mathbb{A}}$ -- number of columns where both characters match
- $\mathrm{ms}_{\mathbb{A}}$ -- number of columns where there characters are different (mismatches)
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Using the same argument as with 2 parameters, how many polygons are possible when all 4 parameters are free?

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- $id_{\mathbb{A}}$ -- number of gap characters (indels)
- $gp_{\mathbb{A}}$ -- number of gaps

Using the same argument as with 2 parameters, how many polygons are possible when all 4 parameters are free?

- how many values of $\mathbf{mt}_{\mathbb{A}}$ and $\mathbf{ms}_{\mathbb{A}}$ can there be for a single input?
- *$O(m^4)$*

Later work shows that this bound can be reduced to $O(m^{d+1/d-1})$